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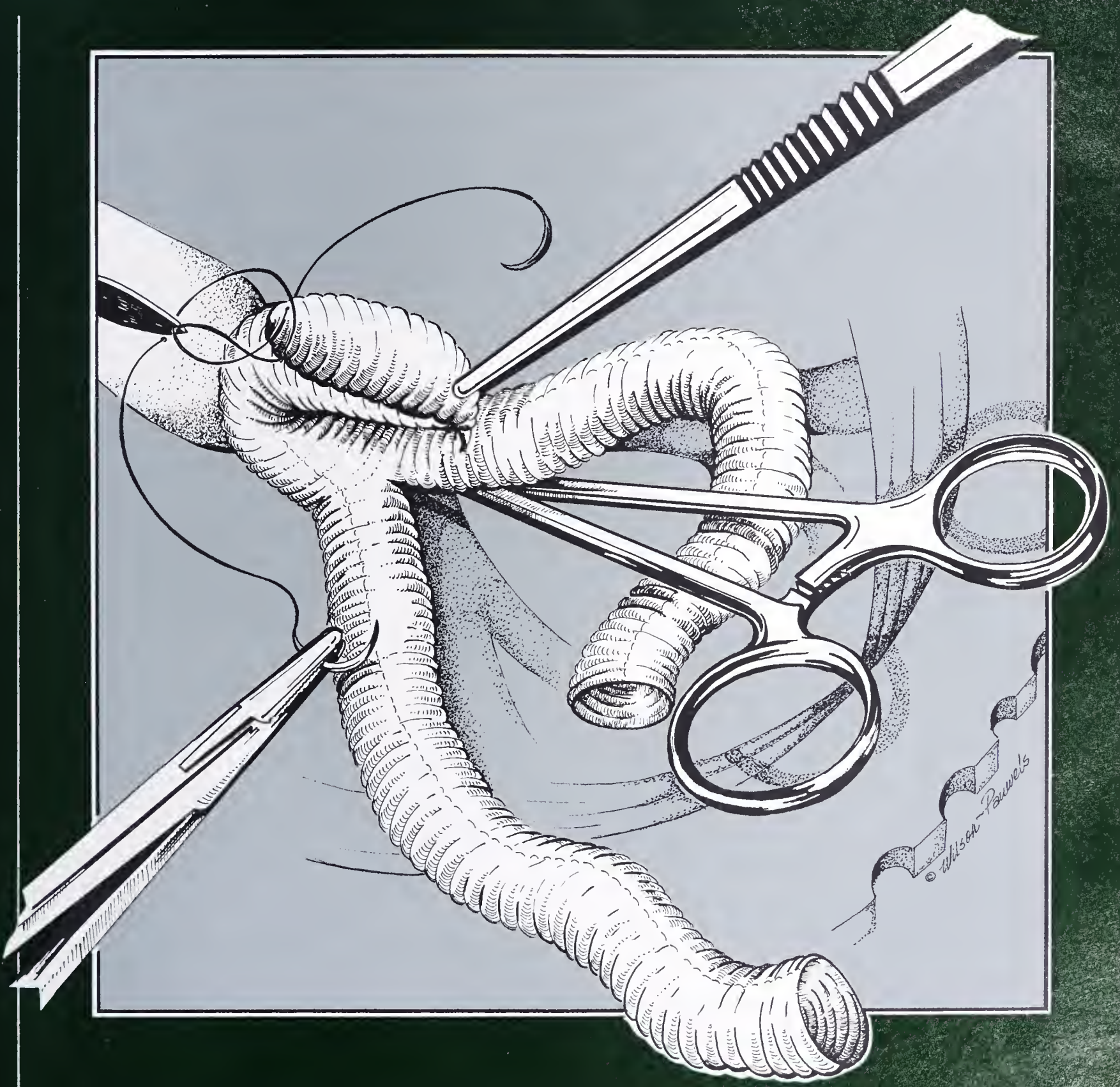

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- *Opthalmology*
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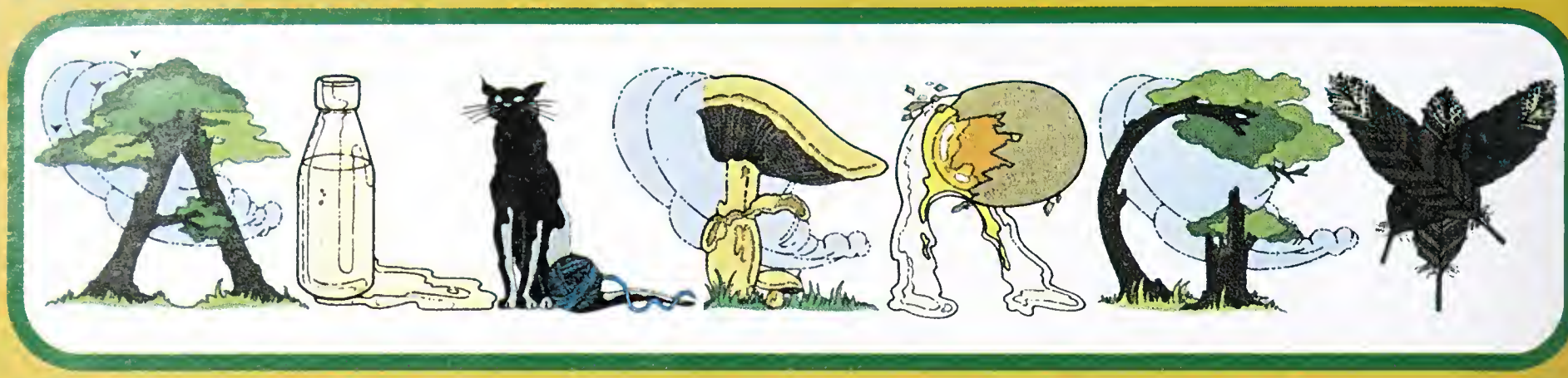

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Arts As Applied to Medicine
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The Medical Alumni Association is the bridge between the graduates and the Faculty of Medicine, University of Toronto.

During your undergraduate years, the Association was involved with providing financial assistance (scholarships, bursaries, travel grants, fellowships, loans) as well as sponsoring programs that were of particular interest — General Practice Panel, Arts and Letters Committee, Undergraduate Affairs, Graduation Banquet, etc. Now that you have graduated, the Association is still able to offer financial assistance in form of bursaries and loans; as well as being your representative at the Faculty and University level.

At the Faculty level, there are two representatives on the Faculty Council, a representative on the Admissions Committee, and the Chairman of the Student Aid Committee is a representative on the Student Awards Committee.

At the University level, the Association has two representatives on the University of Toronto Alumni Association, two representatives on the College of Electors, and a representative on the Varsity Fund Executive Committee.

We are also represented on various Search Committees when Department Chairmen and the Dean of Medicine are being sought.

During the past three years the Association has been involved in collecting funds on behalf of the Faculty of Medicine (Update) to support and expand a Continuing Education program. This program will become increasingly more important if the College of Physicians and Surgeons decides to incorporate the need to re-license physicians every five years. Government funding has been decreased for existing programs, and there is no provision for the incorporation of new ones.

The Association is also involved in providing some impetus to five year reunions. Two letters will be sent free of charge, for each class celebrating their reunion. Every attempt is made to keep an up-to-date address list of all our graduates. Please remember to notify YOUR Medical Alumni Association of any address change.

The Association is governed by graduates who give their time and talent voluntarily. There is one full time employee. Donations given for Student Aid are used entirely for that purpose; and the donations given on behalf of the Faculty of Medicine Update are tuned over to the Faculty without any administrative charge. Trust funds are administered, without charge, following the direction of the donor.

If you are interested in serving on the Executive Committee, or would like to have your opinions voiced to the proper authorities, please do not hesitate to contact YOUR Medical Alumni Association.

Above all, consider it an honour to be invited to attend the Medical Alumni Association and to help those who are coming after you.

MEDICAL ALUMNI ASSOCIATION

Editor's Message

This, the third issue of the 62nd volume of the *University of Toronto Medical Journal*, will be the last issue of this academic year (1984/85). The *Journal* will be continue with Volume 63 in September, 1985 as the new editorial staff take over for the academic year 1985/86.

We conclude the 62nd volume with many interesting articles ranging from neurophysiology to cardiovascular surgery, including an article on Computers in Medicine.

It has been a challenging and rewarding experience for me in editing the Journal this year. I would like to thank the Associate Editors and the Editorial Staff who have given generously of their time. I would like to extend my special appreciation to Mrs. A. Randall for her kind advice and support. In addition, my appreciation goes to Mrs. Mary Eng of Centurion Publishing for her boundless energy in typesetting and printing the Journal.

I would like to congratulate this year's authors for the fine articles they produced and Art as Applied to Medicine for their thoughtfully drawn covers.

Lastly, I would like to thank my friends and classmates for their encouragement and support throughout the year.

Vincent W.S. Lai 8T6
Editor-in-Chief

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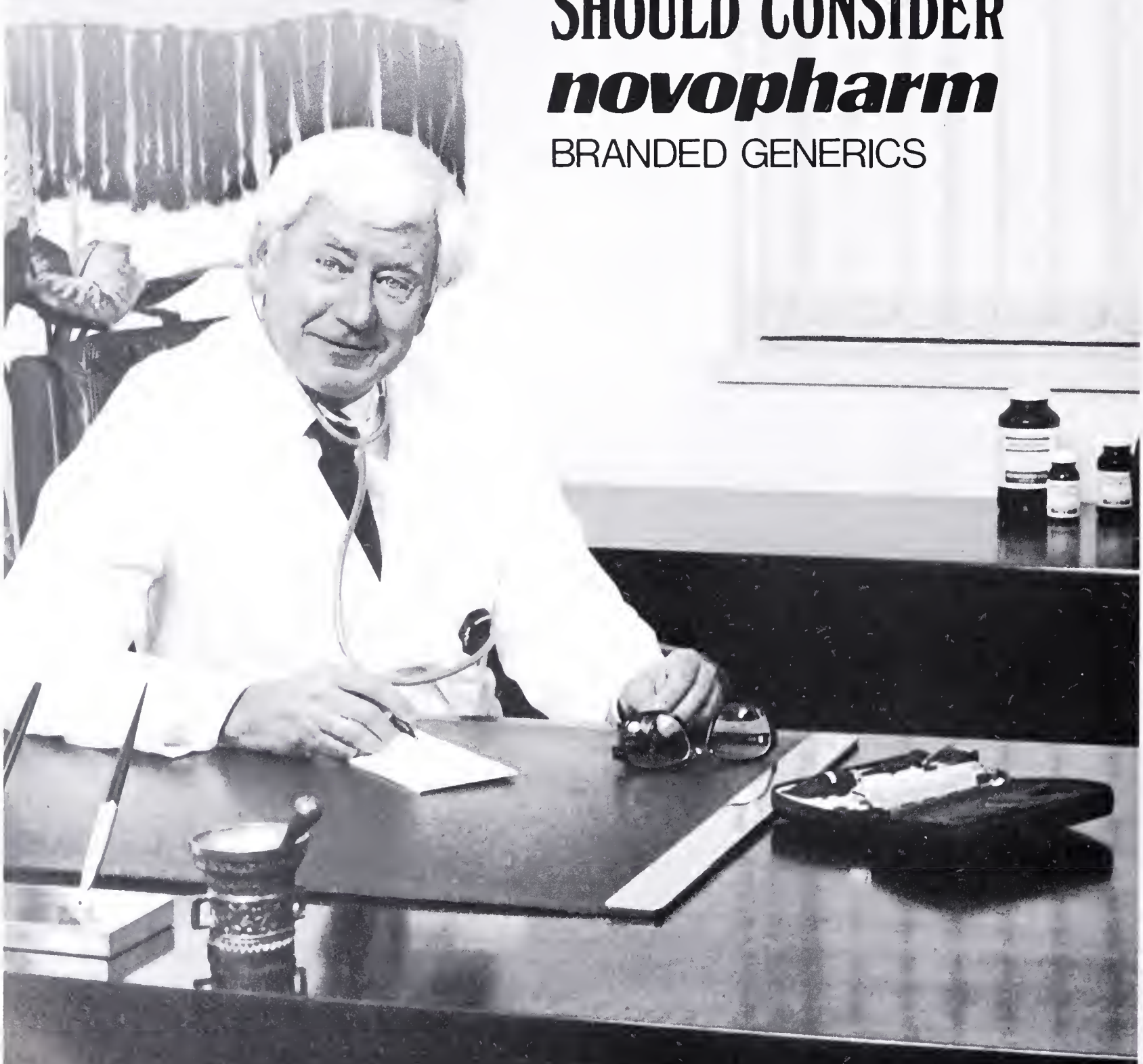

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FEATURE ARTICLE:

Traditional Chinese Medicine: An Ancient System of Healing

Vincent W.S. Lai 8T6

According to legend, traditional Chinese medicine first emerged as a system of healing some five thousand years ago (c.3000 BC), during the period of the "Five Rulers". Although no accurate historical records exist of this period, historians generally agree that two highly respected and widely used medical texts, the Nei Ching (or Classic of Internal Medicine) and the Pen Ts'ao (or The Herbal), were first written during this period (c.1000 BC) and were modified through the centuries. The first accurate historical account of traditional medicine dated back to the third century BC in Szu-ma Ch'ien's Historical Records. Many important figures in traditional medicine have been mentioned in historical works including Pien Ch'iao (the Father of Anesthesia), Ts'ang Kung, Chang Chung-Ching (the "Chinese Hippocrates"), Hua T'o, Ko Hung, Sun Szu-Miao and Li Shih Chen. Their accomplishments and writings contributed to and modified traditional Chinese Medicine to the form which is used today by traditional practitioners. Traditional medicine presents an approach to illness, its diagnosis and treatment based on the Yin-Yang doctrine which is central to traditional philosophical thought. During the past few decades, an effort has been made to test the efficacy of traditional therapy under scientific conditions. The results in many instances prove encouraging. Indeed, in the People's Republic of China, traditional medicine is used in conjunction with modern western medicine for many illnesses with studies showing better results than with western medicine alone.

The Chinese art of healing first emerged, as a natural extension of ancient Chinese literature, art, and philosophical thought. Medical texts dating from as early as one thousand years BC have been and still remain today as the cornerstone of traditional Chinese medicine based on herbs and acupuncture. Traditional medicine was built on a foundation of empiricism, without the intense theoretical investigations required in western medicine. Thus, many tried-and-true techniques have been passed down through the generations for thousands of years, being modified and refined along the way; and to this day, traditional Chinese medicine is practised in China much as it was in ancient days. During the last few decades, physicians and scientists trained in modern western medicine have rigidly scrutinized traditional medicine and found traditional therapy effective in many instances. In fact, some drugs used in modern medicine in the western world today have originated from Chinese herbal medicines which were discovered to be efficacious thousands of years ago. The following briefly summarizes highlights of Chinese medical history, the traditional approach to illness and diagnosis and finally, important aspects of recent research into traditional therapy.

History of Chinese Medicine

Legend has it that Chinese medicine began during the period of the "Five Rulers" of China of which three were considered the founders of the art of healing. This period was roughly 3000 BC. Fu Hsi, the first of the three rulers, who lived c.2900 BC, formulated the Doctrine of the Two Principles called yin and yang which are central to the logical structure behind Traditional medicine. This doctrine generated Fu Hsi's *Pa Kua*, or *Eight Diagrams*, which formed the basis for the oldest Chinese book, the *I Ching, (Book of Changes)*. Shen Nung, the second of the three rulers, who lived c.2700 BC, was called the Fire Emperor. He is recognized and still worshipped in Chinese temples as the father of both Chinese medicine and argriculture. He is credited with the invention of the plough. It was believed that Shen Nung examined, experimented with and personally tasted hundreds of different herbs in the forests and marshes of Lieh Shan. From these investigations, he wrote the first *Pen Ts'ao (The Herbal)* which enumerates 365 drugs. Huang Ti, the third of the three rulers who lived 2600 BC, was known as the Yellow Emperor. He was credited with the invention of the first wheeled vehicle, ships, currency, music and acupuncture. According to traditional beliefs, Huang Ti along with one of his minister, Ch'i pai, wrote the *Nei Ching (Classic of Internal Medicine)*, the oldest and most venerated of all Chinese medical works. The *Nei Ching* still holds a high place among Chinese physicians today who practice traditional medicine. The book covers topics such as acupuncture, principles of the pulse and pulse indications, the theory of disease, diseases such as malaria, diabetes, nephritis, bronchitis, gastric ulcer, measles and cholera, and principles of treatment.

The Historical Period

The first physician to be mentioned by historians was Pien Ch'iao who lived c.407-310 BC during the Chou Dynasty and

considered the Father of Anesthesia. He introduced the use of soporifics, intoxicants and other sedatives for the treatment of pain. He was also skilled in the techniques of pulse palpation and acupuncture. Szu-ma Ch'ien, a historian, wrote in his *Historical Records* of some interesting cases involving Pien Ch'iao including his diagnosis and treatment with acupuncture of catalepsy in a Prince who was erroneously pronounced dead. The *Nan Ching* (Difficult Classic) is a work written by Pien Ch'iao and is basically an elucidation of eighty-one difficult passages from the *Nei Ching*. Chinese medicine reached the pinnacle of its development during the Han dynasty (206 BC-220 AD), a period during which China's influence spread around the world via the Silk Road and the Burma Road. During this period, three men advanced Chinese medicine: Ts'ang Kung, Chang Chung-Ching and Hua T'o

Ts'ang Kung (born c.215 BC), was the first to objectively record clinical case studies. In his treatment of diseases, Ts'ang Kung used mostly drugs and on occasion acupuncture. Throughout his case studies, Ts'ang Kung kept his objectivity and admitted both his triumphs and failures. Chinese medicine at this time placed much emphasis on obstetrics since population growth was of prime importance in the early years of the Han dynasty when they were recovering from wars. Ts'ang Kung was known for employing drugs to hasten labor.

Chang Chung-Ching (born c.160 AD), was regarded as the greatest of Chinese physicians and often called the Chinese Hippocrates. He furthered Chinese medicine by emphasizing diseases from a clinical standpoint based on physical signs, symptoms, progression, methods of treatment and action of drugs. His work, the *Shang Han Lun (Essay on Fevers)*, is one of the most important Chinese medical works. The *Shang Han Lun* contains many essays on rules for treating disease and prescriptions for drugs. Antipyretic treatment of fevers was in the form of drugs and hydrotherapy. This work was the earliest advocating the use of enemas for the treatment of the constipation of typhoid fever. During the 1800 years since the *Shang Han Lun* was written, at least 115 commentaries, concordances and editions have been published and the popular editions still remain today as the bedside book of the traditional Chinese physician.

Hua T'o was China's greatest surgeon (born c190 AD). Although Pien Ch'iao had used anesthetics four centuries prior, Hua T'o was the first to combine expertise in both anesthetics and surgery. As a surgeon, he invented sutures and was the first to use antiseptics, antiinflammatory ointments and antihelminthics for ascarides. Hua T'o administered an effervescing powder in wine which produced anesthesia and he would perform laparotomies and wash, cut or remove diseased portions of organs. After suturing the parts together, he would apply a salve to the wound and the patient recovered after a month. Hua T'o was also the first to realize the value of regimented exercise for good health and formulated a series of exercises called the frolics of the five animals. He was also the pioneer of medicinal baths and hydrotherapy. Unfortunately, Hua T'o never published his own works but many of his accomplishments were recorded in the historical works, the *Wei* and *Han Annals* and the *Chronical of the Three Kingdoms*. Except for these works, no Chinese history books have ever recorded the use of drugs for anesthesia nor major operations since the death of Hua T'o. Confucian philosophy held the body sacred and post mortem dissections were forbidden, thus surgery did not progress.

The 3rd to 6th century AD marked the pinnacle of Taoist influence. One of the great Taoist physicians was Ko Hung (281-340 AD) who was the first to accurately describe small pox and its treatment. His medical texts include the *Chin Kuei Yo Fang (Medications from the Golden Box)* and *Chou-Hou Pei-Tsi Fang (First Aid Measures)*.

After the decline of the Han dynasty, the Sui and Tang dynasties saw rapid development in national culture and economy. In 624, the study of Chinese medicine was approved by examinations under the control of the T'ai i shu (Grand Medical Service). It is one of the earliest examples of the teaching of medicine under state control. Sun Szu Miao (581-682) was an important physician of the period. His works on herbal medicine include *Ts'ien Chin Fang (1000 Precious Recipes) and Ts'ien Chin I (Supplement to 1000 Precious Recipes)*. With the fall of the Tang dynasty, the Northern Sung dynasty (960-1126) was not able to achieve a unification of Chinese territories. Eventhough the period saw weakness in the political and military sense, the advancement of medical knowledge was great. New crude drugs entered the Chinese pharmacopeia and encyclopedias were printed containing a compilation of medical articles.

With the invasion of the Mongols and the establishment of the Yuan dynasty (1279-1368), China faced a period of devastation. The population suffered and decreased significantly. There were no advances in medicine during this period. A peasant revolt brought on the Ming dynasty (1368-1644). Li Shih Chen (1518-1593) was an important physician of this period. His work the *Pen Ts'ao Kang Mu* is as highly regarded as the *Nei Ching* and is considered the only important work after the Yuan dynasty. This work gives a comprehensive account of Chinese material medica in an organized fashion classifying them into mineral, vegetable, and animal products.

During the Ch'ing dynasty (1644-1911), Protestant missionaries first brought western medicine to China. During the early 20th century, there was significantly movement towards western medicine among the cultivated elite who have studied or traveled abroad; although, the peasants still trusted traditional medicine. During this period, traditional medicine was overshadowed by western medicine. However, with the rise to power of the communists, traditional medicine was restored to official esteem.

The Approach in Illness and Diagnosis:

Chinese medicine remains an enigma to most westerners unless one is intimately aware of Chinese culture and philosophical thought. For it is this philosophy of the universe that is the basis of the traditional Chinese perception of the human body and illness which is as different from western concepts as the Chinese language is different from the English language. These different perceptions form a coherent and logical foundation for an alternative approach to health and disease. In traditional Chinese Medicine, there is no nervous system, yet Chinese medicine can treat what modern

western physicians call neurological disorders. The Chinese refer to certain disorders as due to "Dampness", "Heat" or "Wind". There is no such disorder as "Dampness" in modern western medicine, yet it can treat what Chinese medicine describes as "Dampness of the Spleen". The terminology used in Chinese medicine cannot be equated to that of modern western medicine.

The traditional Chinese physician approaches the patient in a holistic manner including both the physical and psychological. A "Pattern of Disharmony" is obtained through information regarding the patient's general characteristics as well as symptomatology. In contrast to Western medicine, Chinese diagnosis does not reveal a specific etiology or well-defined disease entity but rather it gives a description of the whole person in a state of imbalance fitting into a "Pattern of Disharmony". Thus, instead of having a peptic ulcer, a patient may be diagnosed as having the pattern of "Exhausted Fire of the Middle Burner".

The basic principle behind traditional Chinese Medicine is the Yin-Yang Doctrine. According to the *Nei Ching*, "the Yin-Yang principle is the basic principle of the entire universe. . . it brings about all change. . . through their interactions and functions, Yin and Yang, the negative and positive principle in nature, are responsible for the diseases which befall those who are in rebellion against the laws of nature." Yin is the complementary opposite of Yang. Yin is associated with cold, rest, inactivity, passivity, darkness, inwardness, interiority and female gender, whereas Yang is associated with heat, stimulation, movement, vigor, lightness, outwardness, exteriority and the male gender. Five principles govern the Yin-Yang doctrine. Firstly, all things in the universe have a Yin and a Yang. In medicine, Yin illnesses are those characterized by weakness, slowness, coldness and underactivity while Yang illnesses are characterized by strength, hyperactivity, and heat. Yin represents the anterior, superior aspects and the outer parts of the body while Yang represents the posterior, inferior aspects and the inner organs of the body. Secondly, each Yin or Yang can be further divided into Yin or Yang. For example, heat (Yang) maybe divided into extremely hot (Yang) and warm (Yin). Thirdly, Yin and Yang cannot exist separately. Thus, heat can only be recognized as heat if cold existed. Fourthly, Yin and Yang control each other. If there is too much Yin, there is not enough Yang. If it is too cold then there is not enough heat. Fifthly, all phenomena are constantly changing their Yin-Yang equilibrium. Yin and Yang transform into each other subtlely and harmoniously as in normal situations or disharmoniously in which the relative proportions of Yin and Yang are in disequilibrium as in the disease state. As Lao-Tzu describes the normal transformation process, "In order to contract, it is necessary first to expand. In order to weaken, it is necessary first to strengthen." Thus normally, periods of activity (Yang) must be succeeded by periods of rest (Yin). If there is too much rest and not enough activity, there will be an excess in Yin and a deficiency in Yan resulting in an imbalance and consequently a disharmonious pattern.

The Yin-Yang doctrine is central to Chinese philosophical thought and thus the Chinese understand and explain phenomena differently than westerners. In western thought, one does not really understand a phenomenon until one knows its cause whereas in Chinese thought, the concept of causation is absent. For the Chinese, phenomena occur independently and not due to any specific cause. That is why the traditional Chinese perception of the human body and the diagnosis of illnesses are so different from western perceptions. But, like western medicine, traditional Chinese medicine has a logical system of thought and method of approach. According to Kaptchuk, it "is grounded in conscientious observation of phenomena. . . It has a body of knowledge with standards of measurement that allows practitioners systemically to describe, diagnose and treat illnesses. Its measurements however, are not the linear yardsticks of weight, number, time and volume used by modern science, but rather images of the macrocosm"[1] — the macrocosm embodying the Yin-Yang doctrine.

Diagnosis in Chinese medicine seeks to determine the Yin-Yang state of the body and employ the "*Four* Examinations": *Looking, Listening* and *Smelling, Questioning* and *Touching*. In *Looking*, emphasis is placed on the physician's first observations of the patient. The patient is classified into Yin-Yang categories according to body characteristics such as energy, shape and color. Yin represents the passive, narrow and tall. Whereas Yang represents the active, broad and short. The physician also looks at facial color and the tongue. *Listening* to the sounds a patient makes as well as *smelling* the presence of any odors is important. *Questioning* the patient is like taking a history. The symptoms revealed by Questioning are also classified into Yin and Yang. Yin symptoms include loss of appetite, excessive sleeping and easy tiring. Yang symptoms includes aches, pains, temperature, chills and sweating. In *Touching*, the physician feels for temperature and water content, abdomen diagnostic acupuncture points and pulse. *Palpation* of diagnostic acupuncture points reveals the hypo- or hyperactivity of the corresponding organs. Pulse palpation is the most important part of the examination. Pulses are taken at the radial artery and are classified according to the depth at which they are felt (superficial, middle or deep in relation to bone), speed, width, strength, shape, length and rhythm. More than 28 basic pulses may be felt by the traditional Chinese physician.

Thus, based on the "Four Examinations", the Chinese physician describes the disharmony in the patient and initiates treatment. The mainstay of Chinese treatment are herbs and acupuncture. For thousands of years, the Chinese have been diagnosing and treating illnesses in such a manner. For the Chinese, traditional medicine has been very effective.

Research into Traditional Methods:

Many trials have been performed since the 1950's on traditional therapy. Most of these trials were conducted in the People's Republic of China and fit into three categories: the first involves the use of traditional therapy on patients already diagnosed by modern Western techniques as having a specific "western" disease; the second involves testing traditional therapy on animals and the third involves *in vitro* investigations on the activity of different herbs.

For example, one study entitled "Clinical Observations of Traditional Chinese Medical Approaches to 65 Cases of Ulcers"[1] involved the treatment of patients diagnosed by modern western methods as having symptomatic peptic ulcer

with traditional medicine. The Chinese physician examined the patients and recognized six different Patterns of Disharmony and prescribed six different treatments even though there was one illness by modern western methods. The results as assessed by modern western methods were exceedingly good in that 81.5% of the patients showed complete recovery, 13.9% showed improvement, 3% showed no change and 1.5% showed deterioration. Many other similar studies have been performed on common "western ellnesses" such as glomerulonephritis, asthma, angina pectoris etc. Their conclusions demonstrate the continued ability of traditional medicine to effectively treat common human illnesses.

Many studies have been conducted to test the effect of one specific herbal treatment on one specific "western disease". For example, "Traditional Herb, Siegesbeckia orientalis in the Treatment of Hypertension"[1]; in fact, such studies on the traditional herb *Ephedra (Ma huang)* resulted in the discovery of the western drug *ephedrine* in the early 1900's[1]. Chinese belief holds that double blind studies are unjustified because they deprive deserving people of treatment. Thus, one must be cautious about accepting the validity of many of these trials[1].

Chinese animal research has had more stringent controls; for example, a study performed by Chen in Peking involved the treatment of Acute Myocardial Infarction (AMI) in dogs with a traditional herbal mixture *(Codonopsis pilosula, Polygonatum sibiricum, Astragalus membranaceus, Salvia miltiorrhiza, Paeonia obovata* and *Curcuma aromatica)*[2]. AMI's were induced by ligation of the anterior descending branch of the left coronary artery and the effect of the treatment was measured using epicardial EKG (ST segment elevation). The size of the myocardial infarction induced was markedly smaller in the herbal test group compared to the saline control group. Another experiment along similar lines "Cerebral Infarction Improved by Safflower Treatment" by Kuang et al[3] involved the treatment of cerebral infarctions induced in gerbils with the commonly used herb Safflower. The "Stroke Index" was significantly lower in the test animals whereas levels of Norepinephrine, Dopamine and 5-hydrosytryptamine were higher in the test animals.

In vivo studies on pharmacological activity have also helped to further elucidate the mechanism by which traditional herbal medicines work. For example, in the study of the anticancer agent homoharringtonine, 10-hydroxycamptothecin and lycobetaine, clinical trials had been performed in which they were found to be active against some malignancies, and *in vitro* animal studies were conducted in which they were found to be active against experimental tumors.[4] Homoharringtonine, in particular, was active against acute myeloblastic, monoblastic and erythroid leukemias in clinical trials.[5,7] Then, *in vivo* studies were conducted to seek the mechanism of action; the influence of these agents on the cell cycle progression of murine erythroleukemia cells were exam-ined. Homoharringtonine was found to arrest cells mainly at the Gl phase of the cycle whereas hydroxycamptothecin worked mainly at the S phase and lycobetaine worked at the G2 phase.

The purpose of these and other similar studies was to identify those active components of traditional Chinese medicine which are effective in a "western sense". In other words, these herbal medicines have been taken out of the context of traditional medicinal practices and incorporated into western medical practice as potential new drugs.

Today, this has been happening in the People's Republic of China. Since 1958, traditional and modern western medicine were given equal importance in China by the Chinese government. In fact, many studies have shown that the use of traditional treatment as part of an entire schema based on modern western diagnosis and treatment has been better than either traditional or western treatment alone. In the case of Acute Myocardial Infarction and Congestive Heart Failure, the mortality dropped from 20-30% to 10-15% in Beijing, Tienshi, Shanghai and Kwangchou when traditional herbs were combined with western medicine as compared to western medicine alone[2]. In this context, the yin-yang doctrine and traditional concepts of health and disease are totally abandonned and the application of traditional herbal treatment was within a clearly western framework. However, some authors suggest that traditional medicine works best when left in the context of Chinese logic claiming that herbs maybe harmful if improperly used. Since treatment based on Chinese diagnosis is tailored to each individual patient, they suggest that perhaps the more precise use of traditional medicines in this context may be more effective.[1]

Western medicine "probes with laser-like accuracy, penetrating to the microscopic agent of disease in the tissue, the cell, and ultimately the DNA molecule."[1] Often in this western approach, the individual's total and psychological well-being are neglected. Perhaps it is this respect for the total individual and maintenance or restoration of his Yin/Yang equilibrium is the first lesson to be learnt from traditional Chinese medicine.

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Human Bite Wounds of the Hand

Heather Volkert, 8T6
George K. B. Sándor, 8T6

Bite wounds are not uncommon injuries, occurring in up to one percent of patients visiting hospital emergency departments.[1] These injuries require prompt and appropriate treatment to avoid potentially serious morbid complications.

Epidemiology

Human bite wounds occur more often in males than in females, with the highest incidence in the 20 to 25 year age group.[2] According to Marr, they are more likely to occur in the summer than in the winter months. More than one third of human bite wounds are found on the hand. Other common targets include the ears, lips, and nose, and the site appears to be culturally determined.[3] Behaviour during the biting episodes includes participation in aggressive acts and sports activities, attempts to control the airways of seizure victims, and working in institutions for the mentally retarded.[4]

Human bite wounds of the hand occur more often on the right side than on the left, and usually follow a blow to an opponent's mouth.[5] The sharp incisor and canine teeth can produce lacerations of the dorsal aspect of the metacarpo-phalangeal joints of the middle and ring fingers. Classically, a history of human bite etiology may be hard to elicit because of patient denial of the incident. The etiology of the bite wound is very important; dog bites must be distinguished from human bites, cat bites, and the bites of wild animals. Dog bites are more common and tend to become infected less often than human or cat bites. According to Douglas[1], 35 percent of human and cat bites may become infected.

Pathophysiology

Human bite wounds may be classified into the following categories[6]:

I Occlusional
II Fist-strike
III Self-inflicted
IV Traumatic amputation

Fist-strike injuries occur commonly and will be the focus of this paper. When contact is made by the maxillary anterior teeth of the opponent with the patient's fisted knuckles the skin overlying the dorsal metacarpo-phalangeal joint is lacerated (Figure 1). The skin, subcutaneous tissue, fascia, and possibly the synovial tissues may be penetrated by the offending incisor teeth, thus implanting saliva laden with pathogens, dental plaque, and calculus in the wound (Figure 2). The tissues surrounding the laceration, though not penetrated, are certainly victim to blunt trauma. This results in damaged tissue integrity and enhanced susceptibility to microbial invasion.

When the clenched fish is released and the fingers extended, the excursion of the extensor tendons proximally tracts pathogens along the tendon sheaths (Figure 3 and 4). This produces an ideal closed space for the development of anaerobic infections. Inspection of the hand with the fingers extended can be misleading, and grossly underestimate the degree of damage present.

Bacteriology

Human saliva contains up to 10^8 micro-organisms per millilitre. Fourty-two species[6] and up to 224 strains of aerobic or facultative anaerobic bacteria have been cultured from human bites.[7] Organisms commonly isolated from human bite wounds include mixed gram positive and gram negative flora[8], specifically, *Streptococcus alpha* and *beta haemolyticus, Staphylococcus aureus* and *epidermidis, Bacteriodes corrodens,* and *Pasteurella multocida.*[4,6] Other reported contaminants with documented infection include *Actinomycosis*[9], *Treponema pallidum*[11], *Clostridium tetani*[11], *Mycobacterium tuberculosis*[12]. and the Hepatitis B Virus[13].

Case History

A 33 year old caucasian male presented at a University of Toronto teaching hospital on the afternoon of August 20th, 1984. On the day prior to admission the patient had been involved in an altercation during a soccer game, at which time he punched his opponent in the mouth, and knocked out two "front teeth". The patient sustained two lacerations over the dorsum of his left hand, which was subsequently washed. Polysporin was applied to the wounds. The patient became concerned because of continued bleeding, increasing swelling, and decreasing finger mobility. He presented to a community hospital, where he received an injection of tetanus toxoid, and a prescription for penicillin, and was released from hospital. That evening the severity of the pain in his hand increased, in spite of having taken his medication as prescribed. By the next morning his hand had become quite swollen, and the wound exhibited a watery discharge. The patient was next seen at the University of Toronto teaching hospital (Figures 5 and 6.).

On examination, the dorsum of the left hand was swollen, and there were two 1.5 centimeter lacerations over the dorsal aspect of the fourth metacarpo-phalangeal jount. Range of

movement of the metacarpo-phalangeal joint of the ring finger was markedly decreased, being limited to 20 degrees. Sensation in the hand was normal. The patient was admitted to hospital with orders for bed rest and hand elevation. The left hand was soaked in saline four times daily, and washed repeatedly with soap and water. The following intravenous antibiotics were administered: aqueous penicillin G, two million units every four hours, and cloxacillin, one gram every six hours.

Three days later the swelling in the left hand was significantly reduced, and the range of motion of the ring finger was improved. The patient was discharged with a prescription for the following oral antibiotics: cloxacillin, 500 milligrams, and penicillin, 300 milligrams, both to be taken every six hours. He returned for follow up in the out-patient clinic one week following discharge at which time his hand was noted to be healing well.

Discussion

Inadequately treated human bite wounds of the hand can lead to serious complications. These include infectious disease transmission, tenosynovitis, joint sepsis, joint contractures, skin slough[8], deformity due to amputation, and psychosexual aberrations.[2] Prompt and appropriate management is imperative in order to avoid these complications.

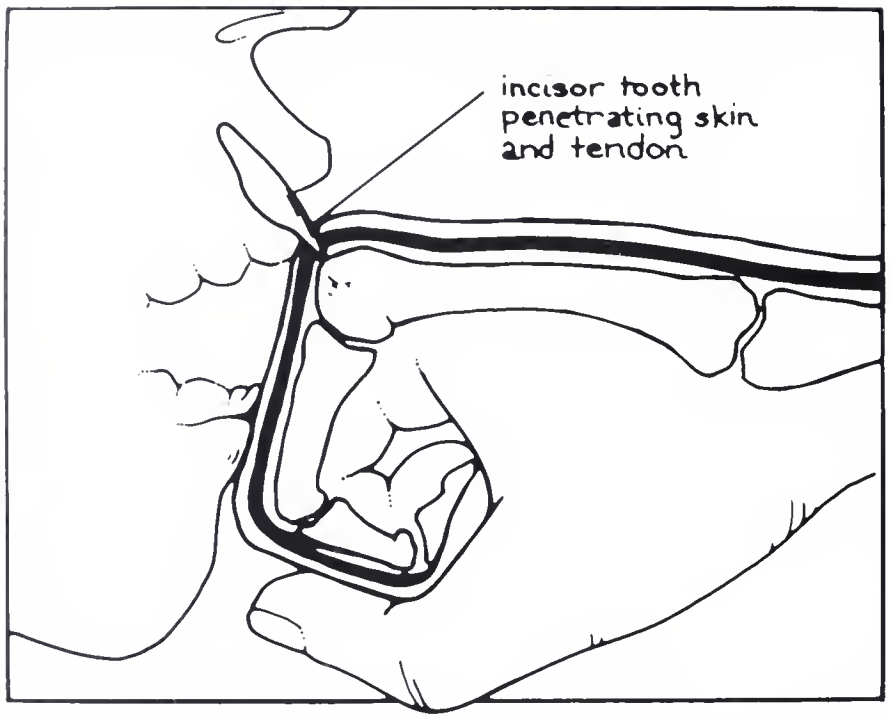

Fig 1. In human bite wounds of the fist-strike type, contact is made with the patient's fisted knuckles, lacerating the soft tissues overlaying the heads of the matacarpals.

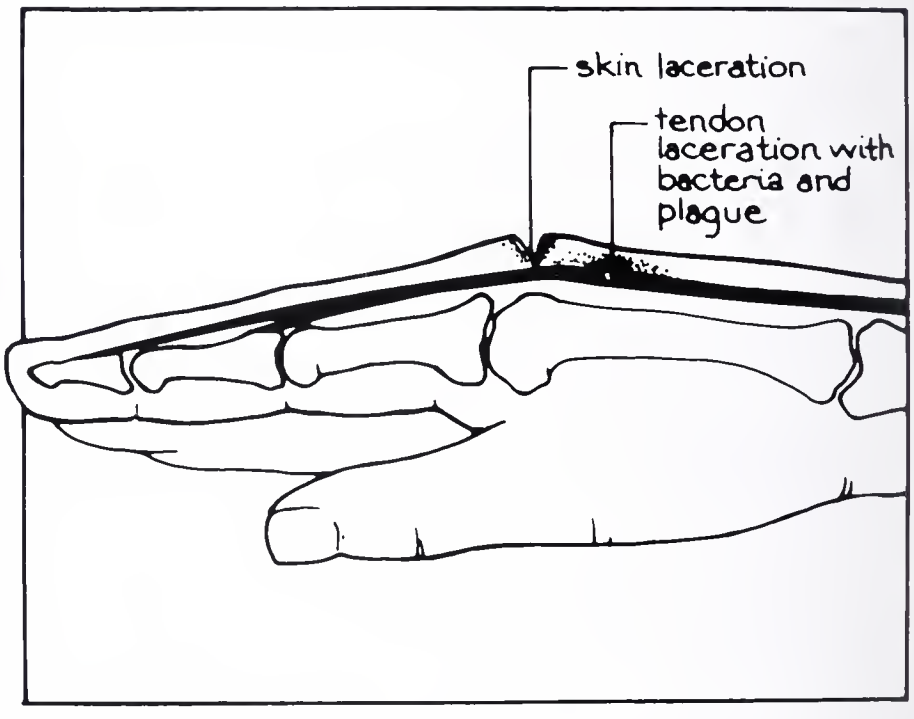

Fig 3. When the clenched fist is released and fingers extended, the proximal excursion of the extensor tendons tracts pathogens and implanted debris along the tendon sheaths.

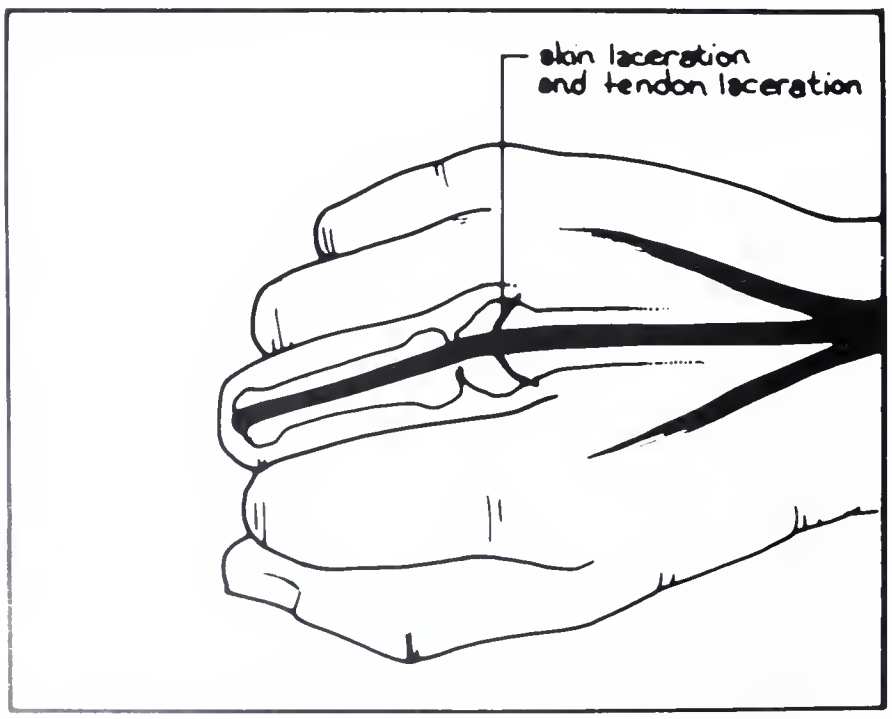

Fig 2. The skin, subcutanneous tissue, fascia, tendons and possibly the synovial tissues may be pentrated by the offending incisor tooth.

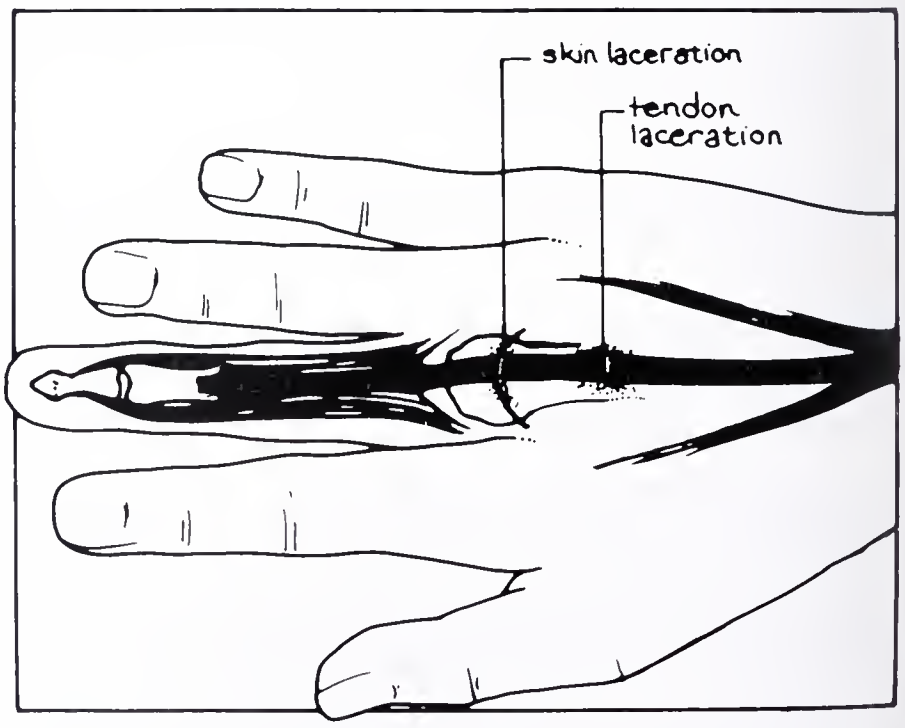

Fig 4. Inspection of the hand with the fingers in an extended position can therefore be misleading.

Fig 5. Lateral view of the left hand showing lacerations over metacarpo-phalangeal joint of ring finger four days after injury.

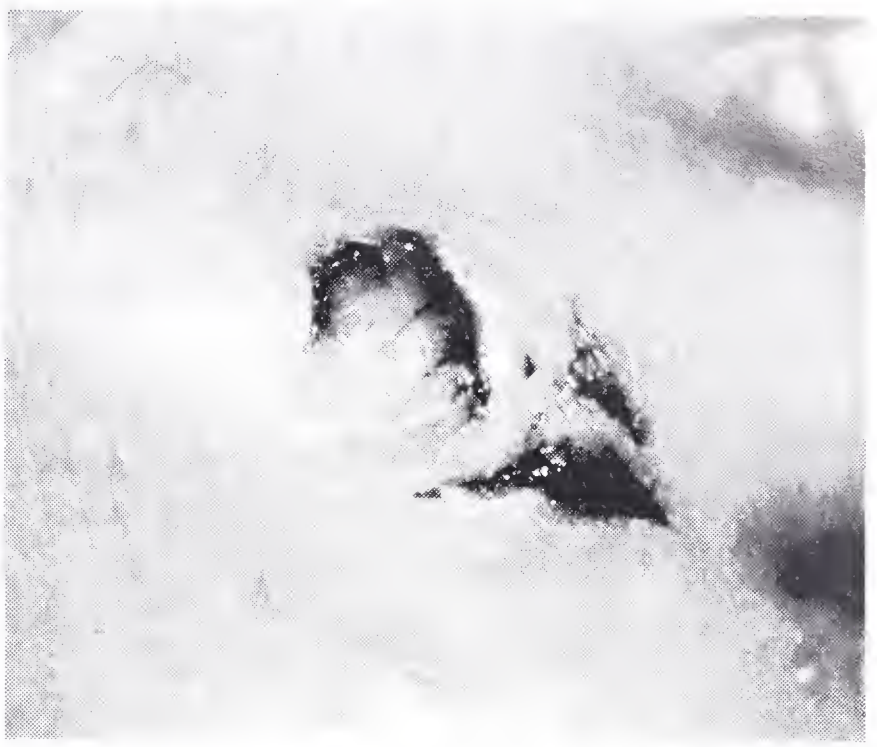

Fig 6. Dorsum of the left hand four days after injury.

On presentation, swabs for culture and sensitivity testing should be taken in all cases, and both aerobic and anaerobic cultures should be requested. The bite wound should be identified and a history of the injury confirmed. All lacerations of the dorsum of the hand should be suspected of being of human bite etiology. The wound should be cleansed and irrigated with copious amounts of saline. Hydrogen peroxide may be useful against the anaerobes contained in some wounds.

The patient should be immediately treated with a course of antibiotics selected to cover the commonly isolated bite wound flora. Recommended antiobiotic coverage includes cloxacillin and ampicillin or cephalexin[1]. For those patients who are admitted for intravenous medications, therapy may be initiated with the above drugs, with or without the addition of an aminoglycoside.[14] In extending coverage to anaerobic bacteria, the addition of metronidazole should be considered. After initial treatment, the antiobiotic should be adjusted to reflect the results of culture and sensitivity testing.

In general, human bite wounds should not be closed with sutures. Those involving the face which could lead to a gross deformity should be seen by a plastic surgeon. Those patients with grossly infected human bite wounds should be placed on intravenous antibiotic therapy and admitted to hospital for prompt irrigation, debridement, and drainage of the wound. In all cases, the patient's tetanus immunization status must be documented, and the appropriate immunization measures taken.

Summary

The pathogenenis and epidemiology of human bite wounds has been reviewed. A case illustrating the presentation and management of this problem has been reported. Initial treatment of suspect human bite wounds must include antibiotic combinations that cover the spectrum of the potentially implanted oral flora. Treatment solely with penicillin has been demonstrated to be inadequate[1]. Those patients with gross degrees of soft tissue injury or with frank clinical infection should be admitted for intravenous therapy. Primary closure with sutures of the human bite wound is to be avoided. Follow-up after initial treatment is mandatory.

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Multiple Bilateral Pulmonary Nodules

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A 55 year old white woman was admitted to hospital in April 1982 for elective investigation of her abnormal chest roentgenogram which had shown multiple pulmonary nodules for an eight year period.

In 1977 her routine chest roentgenogram revealed bilateral lower-lobe nodules. A review of previous films demonstrated one small nodule dating back to 1974. Investigations in 1977 included: two percutaneous needle aspiration biopsies which were both negative for malignancy and infectious etiology, a tuberculosis skin test (positive), a complement fixation for histoplasmosis, coccidiomycosis and aspergillosis, all of which were negative. An IVP and mammogram at that time were reported as normal.

For a twelve-month period in 1978-79 she was treated with INH chemoprophylaxis for tuberculosis. In 1979 she was again admitted to hospital for investigation because of a thirteen pound weight loss. Chest roentgenograms revealed that the previously demonstrated nodules had increased in size. Two needle biopsies were reported to show granulomatous inflammation. No specific treatment was given.

On admission in 1982 she denied chest symptoms except for slight dyspnea with severe exertion. She had a forty pack-year smoking history. Physical examination revealed a pleasant woman in no distress. Vital signs were as follows: blood pressure 170/80, heart rate 84 beats/minute and regular, respiratory rate 20/minutes, afebrile. Abnormal findings included: pinpoint pupils secondary to pilocarpine drops for glaucoma, bilateral carotid bruits, a Grade II/VI systolic ejection murmur, and diminished posterior tibial and dorsalis pedis pulses bilaterally. There were no abnormal findings on chest examination and the remainder of the physical examination was normal.

In-hospital investigation revealed the following laboratory results: hemoglobin 134 g/L, white cell count 3.8 × 10 g/L, ESR 5 MM/h, nonreactive latex fixation for Rheumatoid factor, ECG normal, bronchoscopy normal. Pulmonary function tests showed a moderate obstructive ventilatory defect with slight gas trapping and a normal diffusing capacity.

The chest roentgenogram (Fig 1 and 2) showed bilateral well circumscribed pulmonary nodules in both lungs which had increased slightly in size but not in number since 1979. There was also blunting of the right costophrenic angle but no hilar enlargement was seen.

What is your diagnosis?

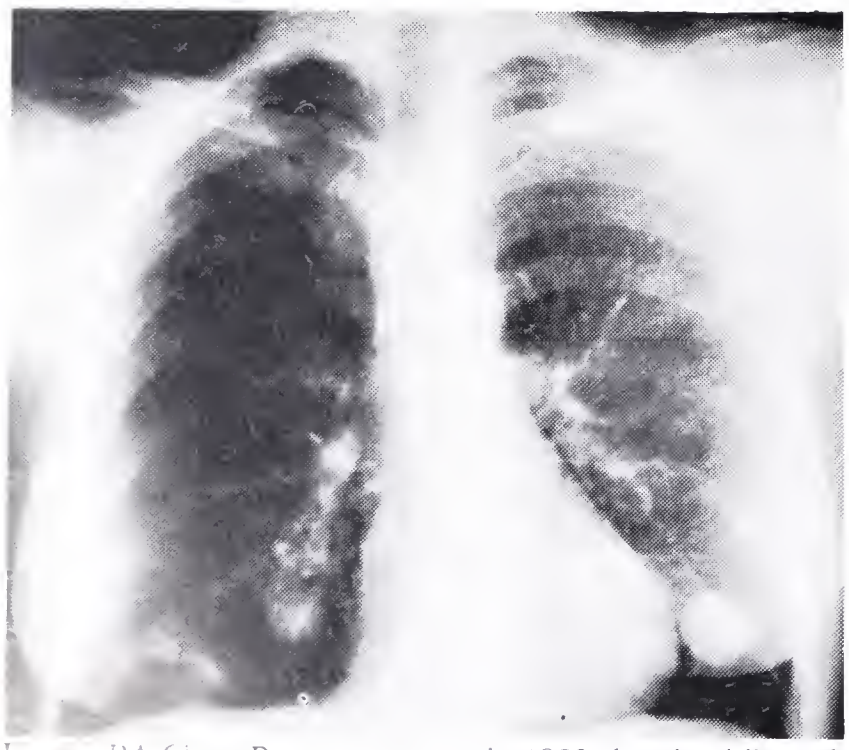

Fig 1 PA Chest Roentgenogram in 1982 showing bilateral nodules.

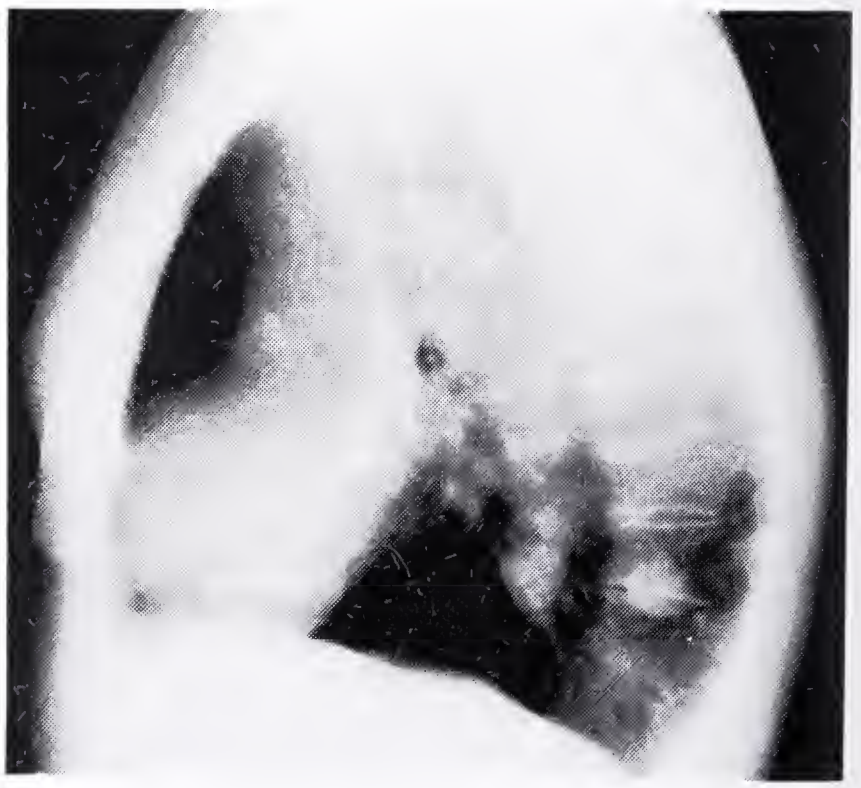

Fig 2 Lateral Chest Roentgenogram from 1982.

An Assessment of Current Techniques of Mitral Valve Replacement: The Effects On Left Ventricular Function — A Summary

Derek C. Archer 8T6
Michael K. McLennan BSc. 8T6
Philip P. Narini 8T6

Recent improvements in general cardiovascular surgical techniques have resulted in a dramatic decline in overall morbidity and mortality from these procedures. However, the incidence of complications from mitral valve replacement (MVR) has remained significantly higher than that from other types of cardiac surgery. MVR involves fixation of the mitral annulus with a rigid prosthesis, and division of the chordae tendinae. The major cause of post-operative complications in MVR is a decline in global left ventricular (LV) function. This study shows that the use of a rigid prosthesis tends to decrease LV function, and that the cutting of the chordae tendinae was a significant factor in the decline of LV function. This investigation suggests that in view of the deleterious effects of severing the chordae tendinae, current techniques of MVR be reassessed to include preservation of the chordae.

Introduction

There has been a dramatic decline in the mortality and morbidity from all cardiovascular surgical procedures in the past few decades. A recent report indicates the mortality for coronary artery surgery is less than 1% (1). Such success can be attributed to advances made in the overall management of surgical patients and improvements in specific surgical techniques (e.g. cardiopulmonary bypass, myocardial preservation, and the advent of prosthetic valves). Although these measures have been effective with respect to mitral valve surgery, mortality has remained significantly higher. In a current report, the mortality has been estimated to be as high as 4.6% (2). A major contributing factor is the impairment of global left ventricular function resulting in a low output syndrome.

The problem of post-operative left ventricular decline is not a new one. This complication has been the subject of many previous investigations. By using the isolated heart preparation, this study eliminated many of the variables complicating these investigations.

It must be remembered that there are many factors inherent to mitral valve disease which cannot be ameliorated by surgery. In contrast to aortic valve replacement, patients with mitral valve disease undergo surgical replacement late in the course of their disease at a stage when the damage to the myocardium is irreversible. Another complicating factor is the inability of the diseased left ventricle to tolerate the increased afterload following correction of mitral regurgitation.

Current techniques of mitral valve replacement usually involve fixation of the mitral annulus with a rigid prosthesis and excision of the papillary muscles and the chordae tendinae. The rigid prosthesis may decrease the effectiveness of the muscle contractions occuring at the base of the heart, and elimination of the contribution of the papillary muscles to the left ventricular preload may be significant. Hence, the disruption of the structural integrity of the left ventricle may lead to a decline in hemodynamic function.

This investigation is designed to study the effects of current techniques of mitral valve replacement on global left ventricular function.

Methods

Fourteen Yorkshire pigs weighing 40-45 kilograms were anaesthetized using Thiopental sodium. The animals were ventilated with 100% oxygen via tracheostomy and intubation. A sternotomy and pericardiotomy were performed. Aortic root pressure was monitored with a catheter inserted in the ascending aorta. In preparation for cardio-pulmonary bypass, the animals were heparinized, the ascending aorta was cannulated via the right carotid artery, and an incision was made from the right atrium to the inferior vena cava. Venous blood from the atriocaval incision was shunted to a calibrated non-pulsatile roller pump, oxygenated, and returned to the cardiac system via the carotid cannula. The aorta was cross-clamped distal to the great vessels in order to complete the isolated heart preparation (fig .1).

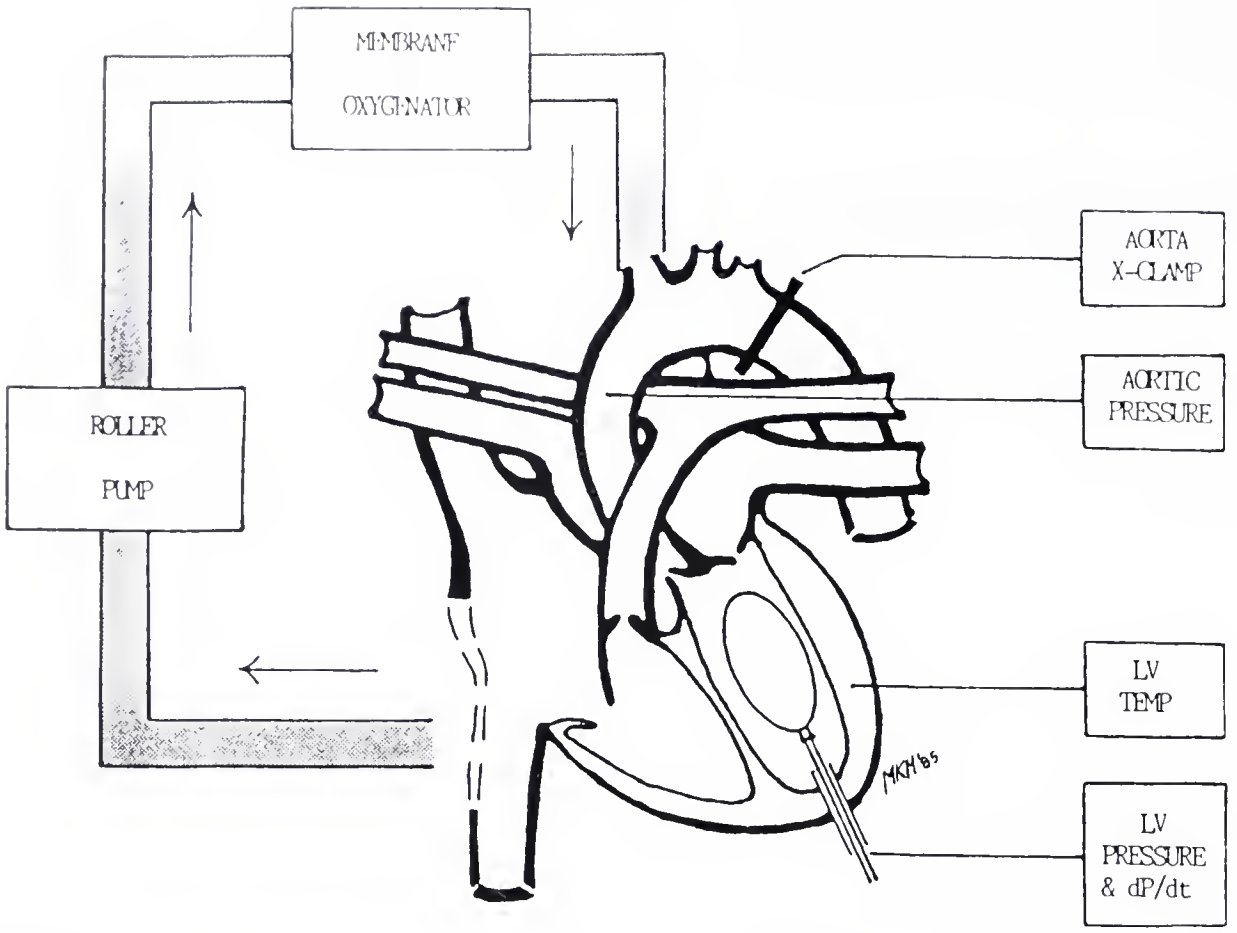

Fig 1. Isolated heart preparation showing cardiopulmonary bypass circuit. Venous blood was suctioned from the atriocaval incision, oxygenated, and returned via the right carotid artery. Left ventricular function was assessed by a compliant balloon inserted through the vent site in the left ventricle. Cardiac temperature was maintained at 37°C.

Pump flow was adjusted to maintain the aortic root pressure at 100 mm Hg. Hematocrit, temperature, pH, and heart rate were maintained at physiological levels.

To prevent air from entering the aorta, a 3mm vent was inserted in the left ventricle and secured with a pursestring suture. The left atrium was opened in order to view the mitral valve. A compliant fluid-filled balloon was inserted through the vent site. This balloon was connected to a pressure transducer via a rigid cannula. The transducer was attached to a pressure monitor, which was coupled with a second monitor, allowing simultaneous electronic calculation and recording of left ventricular pressure and the derivative of pressure with respect to time (dP/dt). The valve of dP/dt is a quantification of contractility. These measurements were made at a balloon volume of 25 ml (Baseline). Pressures generated during systole by the left ventricle were assessed by the calculation of developed pressure (P systolic - P diastolic).

A #23 Bjork Shiley (BS) valve was snared onto the existing mitral valve, and left ventricular function was measured (Rigid Annulus). The BS valve was removed and the chordae tendinae were severed. Left ventricular function was reassessed (Cut Chordae). Simulating the current techniques in mitral valve replacement, the BS valve was replaced. Left ventricular function was measured (Cut + Rigid).

The animals were sacrificed by Thiopental overdose at the termination of each experiment. In all cases, the animals were treated humanely in accordance with National Academy of Science Guidelines.

Results

The results are summarized in figures 2 and 3. The insertion of

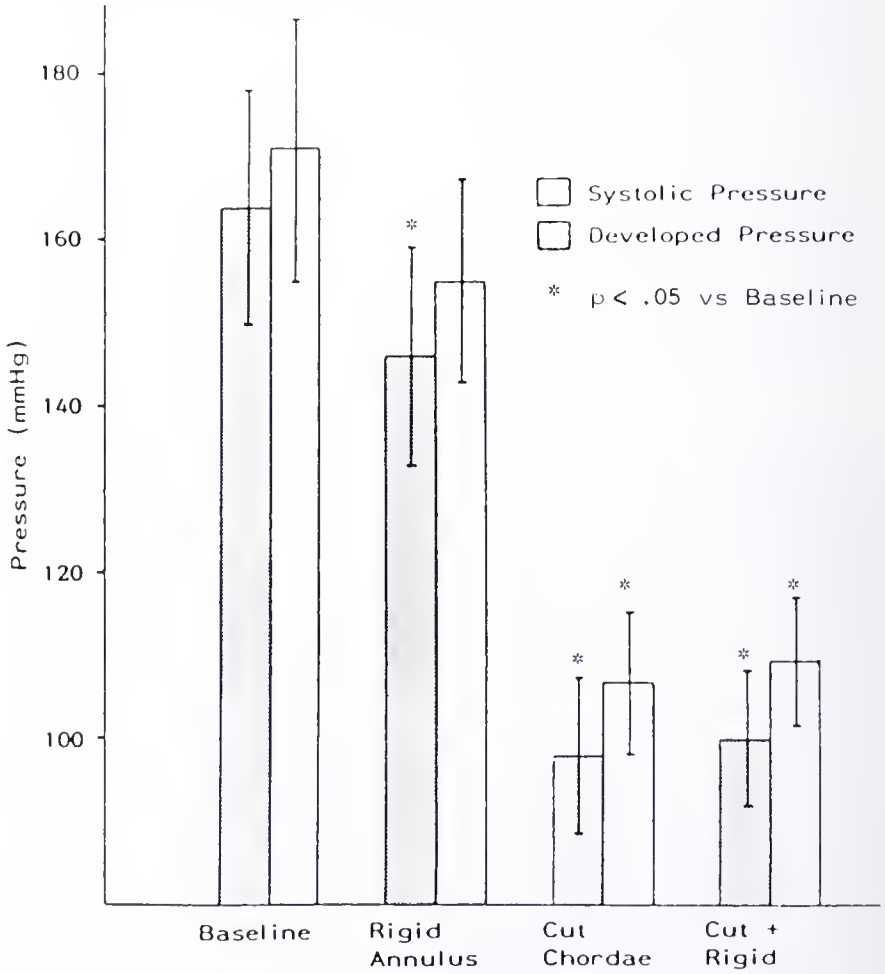

Fig 2. Systolic pressure was slightly reduced (NS) following fixation with a rigid annulus, and significantly decreased when the chordae tendinae were divided with no additional reduction following a combination of the above procedures. Developed pressure was significantly decreased in all three procedures, with the most dramatic reduction occurring following division of the chordae.

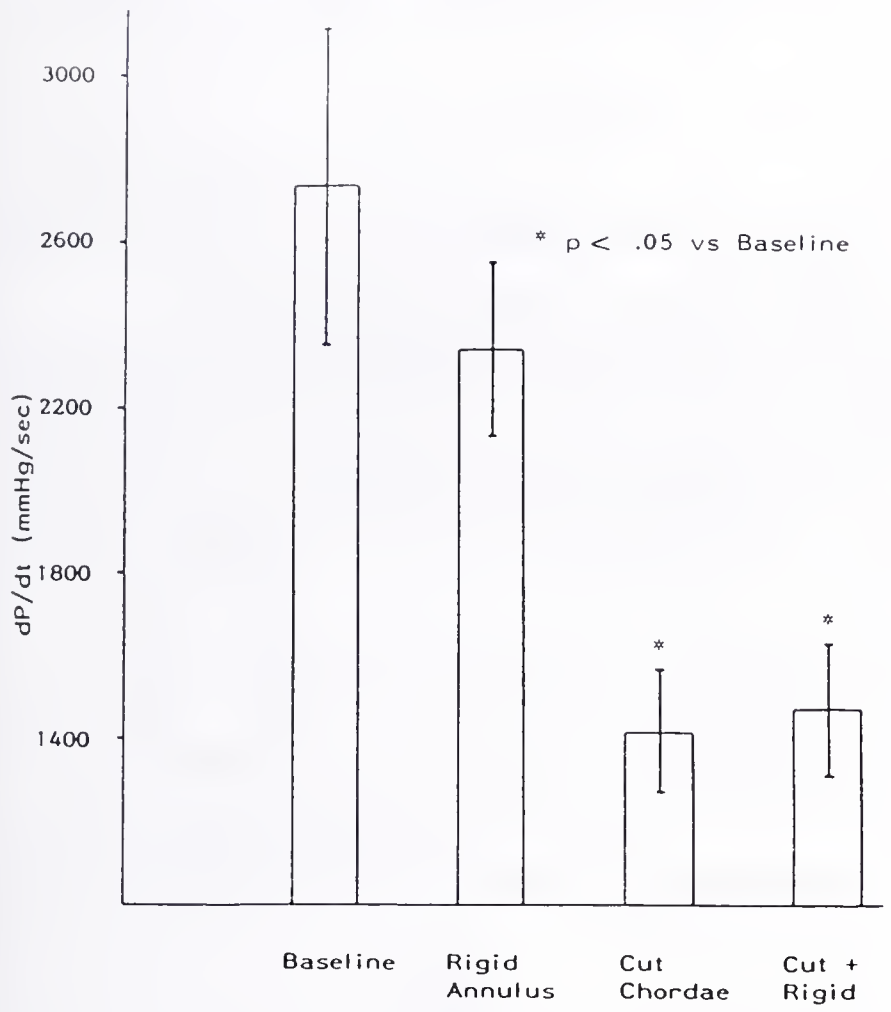

Fig 3. Changes in dP/dt indicated significant decreases in left ventricular contractility following division of the chordae tendinae, with or without fixation with a rigid prosthesis. Insertion of the rigid prosthesis alone showed no significant change.

a valve, either before or after cutting of the chordae tendinae, caused no significant changes in left ventricular function. However, there was a small reduction in systolic and developed pressures as well as contractility. Cutting of the chordae resulted in a large deterioration in left ventricular function - there was insignificant decrease insystolic and developed pressures as well as dP/dt.

Discussion

Over the past decade, there have been many studies designed to assess the problems specifically associated with mitral valve replacement. These studies examined the effects of a mitral valve prosthesis and the papillary muscles on the performance of the left ventricle. While some past investigations have shown a decrease in mortality from the preservation of the chordae tendinae, other studies have challenged these results (3, 4)

Whereas past experiments studied the heart ejecting into an intact peripheral circulation (3), this study was unique in that the heart was isolated from the rest of the body. In this way, many of the systemic factors, such as peripheral vascular changes, local tissue anoxia with enzyme release, and humoral responses, which were sources of discrepancy among past studies, were eliminated. These systemic factors would affect heart rate, cardiac output, blood pressure, preload and afterload, making results difficult to interpret.

The need to design an experiment to eliminate systemic variables created, in itself, its own weaknesses. This procedure monitored only acute changes in left ventricular function. Such a study ignores any adaptive changes that would occur with time. By eliminating compensatory mechanisms, the isolated heart preparation may overestimate the effects of the decline in left ventricular function. Also, this study involved only normal pig hearts. Consequently the artificial situation of a normal heart undergoing mitral valve replacement may not fairly represent the procedures performed on patients with diseased hearts. Most important, the isolated heart in this study was not ejecting. As well as any dynamic parameters this may have affected, changes in left ventricular function could not be related to quantitative values of the clinically important cardiac output and ejection fraction.

The results from experimental fixation of the mitral annulus showed a trend of decreasing left ventricular developed pressures and systolic presures which was not significant. Perhaps an increased sample size may show this trend to be statistically significant. These present results open avenues for future investigations to prove or disprove the hypothesis that a rigid annulus is detrimental to ventricular pump function. If the use of a rigid prosthesis was ultimately proven to be deleterious, this would warrant a reassessment of this procedure in mitral valve replacement. Studies are presently underway investigating the effectiveness of a flexible prosthesis as a viable alternative.

Division of the chordae tendinae resulted in a significant decrease in systolic and developed pressures as well as dP/dt. In an intact heart, depolarization of the left ventricle begins at the endocardial surface. Therefore, the papillary muscles contract prior to the rest of the ventricle. This action results in a shortening of the major axis (base to apex) of the heart during isovolemic contraction. Consequently, the minor axis (perpendicular to the major axis) must increase to maintain the left ventricular volume. Such a lengthening of the minor axis stretches the circular fibres of the left ventricle and the subsequent increase in preload results in an increased contractility, in accordance with Starling's Law of the Heart (5). Cutting of the chordae eliminates the contribution of papillary muscle contraction to the development of left ventricular preload.

In clinical practice, the chordae are sometimes involved in the pathological process of the mitral valve. In long standing disease, the chordae can become calcified. In such a case, it may not be advantageous to preserve them and it might prove to be a time consuming and tedious procedure. It is also possible that in such end-stage cases, the pathology of the chordae and papillary muscles is such that their contribution to left ventricular contraction are minimal. The left ventricle may already have compensated for this loss and thus the preservation of these structures during mitral valve regurgitation would serve little purpose.

Summary

This study evaluated current techniques of mitral valve replacement. The results showed a trend towards a decrease in left ventricular function (LVF) with the use of a rigid prosthesis and a significant decline in LVF with the division of the chordae tendinae. These results warrant a reassessment of current techniques of mitral valve replacement in order to

morbidity and mortality associated with this procedure.

Acknowledgements

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Reducing The Risk of Urgent Surgery for Unstable Angina

Brain Chong, 8T6

During coronary bypass surgery, the heart is arrested to provide a motionless and bloodless field for the surgeon to perform the delicate vein-to-coronary artery anastomoses. Unless protected, the myocardium will suffer ischemic damage. Cardioplegic solutions have been developed to arrest the electrical and mechanical activity of the heart and protect it from ischemic injury. Patients with unstable angina (prolonged episodes of rest angina despite medical therapy) have a high risk of ischemic injury during coronary bypass surgery.

To reduce the risk of ischemic injury during surgery for unstable angina, two alternative methods of preserving the heart were compared in the prospective, randomized trail. Fifty-four patients were randomized to receive crystalloid cardioplegia (CC) and 46 were randomized to receive blood cardioplegia (BC). The results indicated that blood cardioplegia provided superior protection against intraoperative ischemic injury in these high-risk patients.

Introduction

Coronary artery bypass surgery has become the most common operation in North America. The procedure permits restoration of blood flow beyond coronary artery obstructions due to atherosclerosis. The techniques employed for coronary bypass surgery have changed dramatically in the past twenty years and the results of surgery have improved. Since 1978, most cardiac surgeons in Toronto have performed the bypass operation with the heart cooled and arrested. The quiet, bloodless field permits the construction of precise anastomoses to small coronary arteries.

Unfortunately, all current methods of rendering the heart quiescent during cardiac surgery induce some ischemic injury. The extent of injury is usually minor in patients undergoing elective surgery, but may be considerable in patients with unstable angina requiring urgent revascularization. Patients with unstable angina have prolonged episodes of rest angina despite medical therapy. These patients usually require urgent surgery to prevent a myocardial infarction. However, they are at greater risk of complications following surgery because of the ischemic injury they suffer before surgery. Recent studies from the Coronary Artery Surgery Study group[2] and from Stanford University[8] have documented the independent influence of both prolonged episodes of rest pain before surgery and the urgency of surgery on postoperative complications.

Improved methods of perioperative myocardial protection may reduce the risks of urgent surgery in patients with unstable angina. Current methods involve the infusion of a crystalloid cardioplegic solution into the aortic root after application of a cross-clamp onto the ascending aorta (Figure 1). The cold solution contains a high concentration of potassium, which results in immediate electrical mechanical arrest of the myocardium. The technique has been shown to improve the results of elective surgery.[2, 9] The cardioplegic solution is intended to eliminate myocardial metabolic demands in order to improve the tolerance to ischemia. However, patients with unstable angina frequently suffer ischemic injury because their tolerance to ischemia has been severely compromised. Another approach to preservation of the ischemic myocardium is the use of blood cardioplegia. This technique was first described in 1978,[5] but clinical studies have been inconclusive.[1, 3, 4, 6] Blood cardioplegia is intended to provided oxygen and substrate for aerobic matabolism during the period of cardiac arrest. Although improved results have been demonstrated with blood cardioplegia in patients undergoing elective surgery[6], the differences are subtle and not clinically significant. However, the results in patients undergoing elective surgery are excellent, and the incidence of postoperative complications is too small to detect a significant difference. Therefore, a prospective, randomized trial was instituted to compare blood and crystalloid cardioplegia in patients requiring non-elective surgery.

Methods

One hundred consecutive patients presenting for urgent myocardial revascularization because of unstable angina agreed to participate in this prospective, randomized trial. Fifty-four were randomized to crystalloid cardioplegia (CC) and 46 were randomized to blood cardioplegia (BC). Preoperative assessment included: age, sex, the frequency and duration of rest angina, the incidence of preoperative electrocardiographic and enzyme changes with the pain episodes, the time from cardiac catheterization to operative intervention, the preoperative coronary anatomy and the left ventricular function. Operative procedure was performed by the cardiac

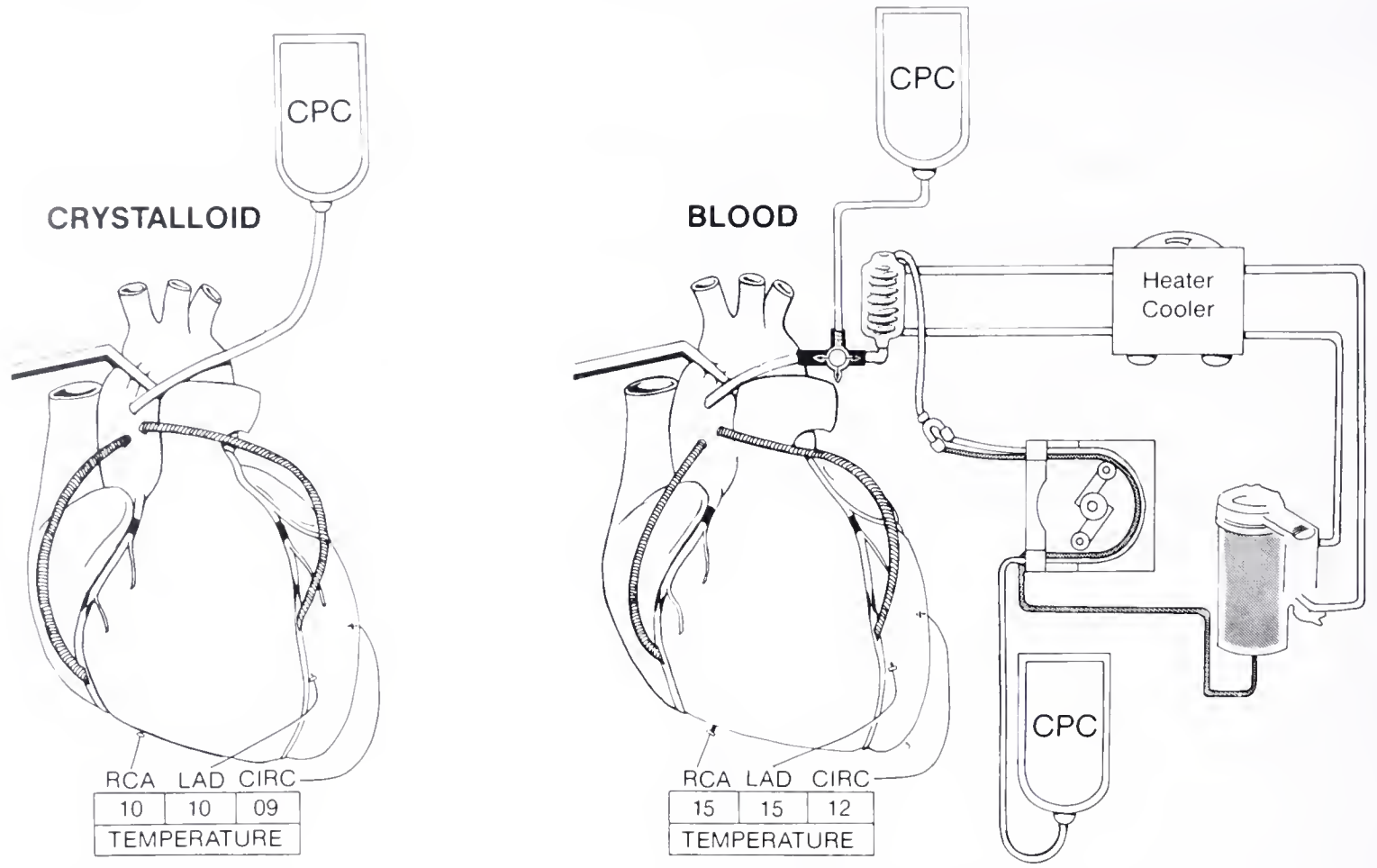

Fig 1. Cardioplegic solutions are delivered through the ascending aorta proximal to the cross-clamp. CPC: crystalloid cardioplegia; RCA: right coronary artery; LAD: left anterior descending artery; CIRC: circumflex artery. Delivery system of crystalloid cardioplegia (CC) A and blood cardioplegia (BC) B with the two saphenous vein grafts bypassing obstructions in the RCA and LAD. Blood is cooled and mixed with the crystalloid cardioplegia solution prior to infusion.

surgeons at the Toronto General Hospital using standard techniques. Figure 1 displays the cardioplegic infusion techniques. Blood cardioplegia was delivered using Buckberg-Shiley Model 502 blood cardioplegia delivery system. Blood from the oxygenator was diluted in a 2:1 ratio with a crystalloid cardioplegic solution in order to establish a final electrolyte concentration similar to the crystalloid cardioplegia. Both blood and crystalloid cardioplegia were delivered into the aortic root at a pressure of approximately 70 mmHg. The blood cardioplegia was delivered at a temperature of 10°C, and the crystalloid solution was delivered at 4°C.

The results of surgery were assessed by evaluating cardiac enzymes, the electrocardiograms and the hemodynamic recovery. Serial measurements of the cardiac isoenzyme CK-MB were made to assess the extent of perioperative ischemia. A perioperative myocardial infarction was diagnosed if the electrocrdiograms showed the presence of a new Q wave (or if a new left bundle branch block or loss of R wave progression was found in association with enzyme elevations). Postoperative low output syndrome was recorded if inotropic medication or the intraaortic balloon pump were required to maintain the blood pressure greater than 90 mmHg for more than 30 minutes postoperatively.

Results

Preoperatively, patients randomized to blood and crystalloid cardioplegia had similar ages, left ventricular ejection fractions, extent of coronary artery disease and incidence of preoperative ischemic electrocardiographic changes. The preoperative AST levels were higher before blood cardioplegia (BC) than crystalloid cardioplegia (CC), suggesting more preoperative ischemia in the blood cardioplegia patients (BC: 54 ± 49; CC: 38 ± 21 IU/L, p 0.05).

Postoperatively, no patient died in either group. Blood cardioplegia patients had less CK-MB released than crystalloid cardioplegia patients (Figure 2). The difference between the curves was statistically significant by an analysis of variance (p 0.01). The incidence of postoperative myocardial infarction was significantly greater in patients who received crystalloid cardioplegia (4/54, 7%) than patients who received blood cardioplegia (0/46, 0%, p 0.05). The incidence of low output syndrome postoperatively was greater in patients who received crystalloid cardioplegia (15/54, 28%) than those who received blood cardioplegia (5/46, 0%, p = 0.08).

Discussion

Previous studies have demostrated that the perioperative mortality and incidence of myocardial infarction are dependent on the severity of the coronary artery disease, left ventricular function, age and sex.[2 8] Patients with left main coronary artery stenosis or diffuse coronary artery disease are at higher risk of surgery. Patients who have diminished left ventricular function, older patients (who may have more extensive coronary artery disease) and females (who have smaller arteries) are at higher risk for coronary bypass surgery. Unfortunately, none of these risk factors can be modified when the patients are presented for surgery. However, the large studies also

found that urgency of surgery and the extent of preoperative ischemic injury were also independent risk factors predictive of outcome. Improved perioperative management may reduce the risks in these patients. With the exception of the AST levels, preoperative variables were similar for the two groups. The higher AST levels in the blood cardioplegia patients suggested that these patients may have been at higher risk, but their results were better. Blood cardioplegia reduced the incidence of myocardial infarction and low output syndrome and reduced the amount of CK-MB released. Blood cardioplegia offered better myocardial protection for patients undergoing nonelective coronary bypass surgery.

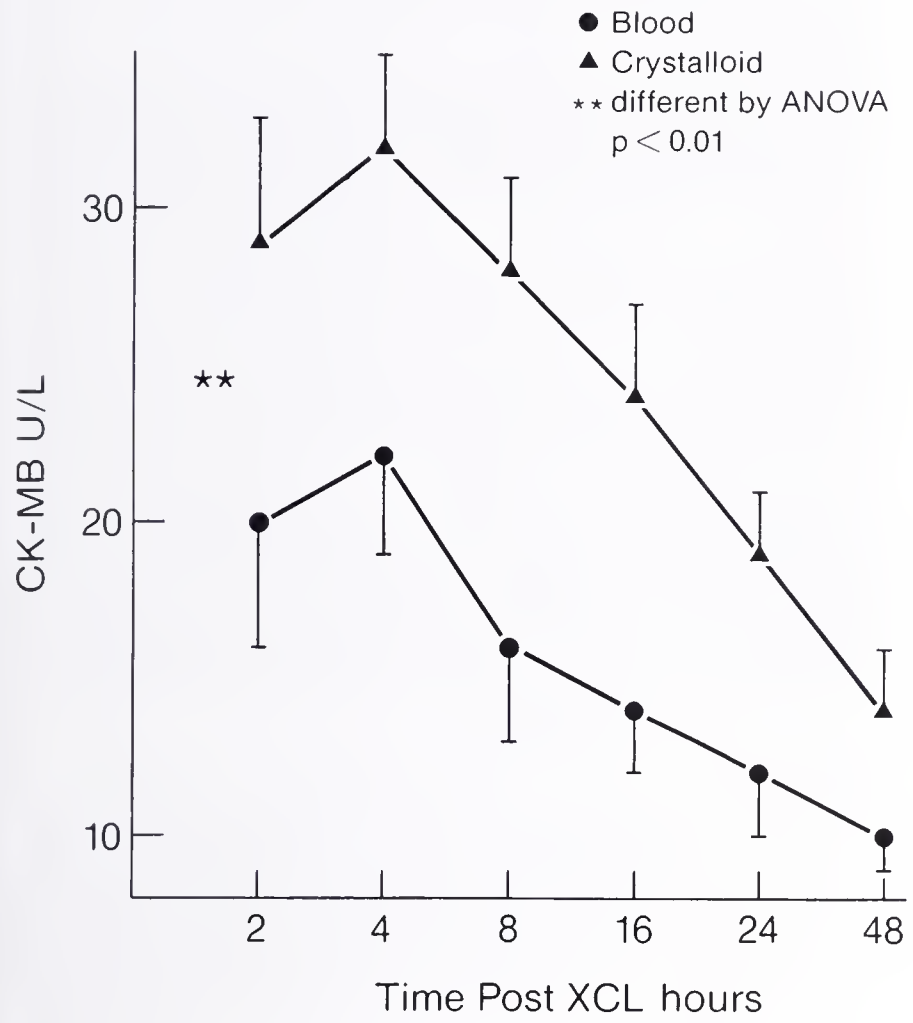

Fig 2. Postoperative serial CK-MB levels for the BC group and CC group were significantly different by an analysis of variance. XCL: cross-clamp; ANOVA: analysis of variance.

Acknowledgements

I would like to acknowledge the support I received from the Heart and Stroke Foundation of Ontario for a scholarship to work with the Division of Cardiovasculat Surgery at the Toronto General Hospital during the summer of 1984. The individuals who conducted the trial presented in this paper include: George T. Christakis, M.D., Stephen E. Fremes, M.D., Jacques G. Tittley, M.D., M. Mindy Madonik, B.Sc, Joan Ivanov, R.N., Jennifer H. McDonough, R.N., C.C.P., Donald A. G. Mickle, M.D., Lynda L. Mickleborough, M.D., Bernard S. Goldman, M.D. and Ronald J. Baird, M.D. I would also like to acknowledge the support of my supervisor, Richard D. Weisel, M.D., and thank Ms. Catherine M. Andrews for preparing the manuscript.

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Predictors of Outcome After Coronary Artery ByPass Surgery for Unstable Angina Pectoris

Arnon M. Katz, 8T7

Introduction

Unstable angina pectoris is the term applied to patients with increasing frequency and severity of their anginal symptoms during the month prior to presentation. The term includes a spectrum of patients with ischemic heart disease. Originally, the term unstable angina was employed for three groups of patients based on their symptoms: (1) new onset angina; (2) crescendo angina (increasing chest pain on decreasing activity); and (3) acute coronary insufficiency (prolonged rest angina, greater than 15 minutes, despite maximal medical therapy).

In the 1970's, a multicentre, prospective, randomized trial was performed comparing medical to urgent surgical therapy for patients with unstable anginsa.[4,5] This study indicated higher mortality and a higher incidence of myocardial infarction in those patients treated surgically. As a result of this experience, medical therapy rather than surgical therapy became the routine therapy for patients with unstable angina. However, patients who were refractory to maximal medical therapy required urgent revascularization in order to prevent myocardial infarction and death. In the 1980's, patients requiring urgent surgery for unstable angina had an increased risk of both perioperative mortality and myocardial infarction. [1,3] In order to improve the results of urgent coronary bypass surgery in these high-risk patients, the factors influencing the outcome must be indentified and modified. A prospective study was commenced in January of 1982 to identify the factors which influence operative mortality and the incidence of perioperative myocardial infarction.

Patient Population

Between January of 1982 and December of 1983, 1,302 (consecutive) patients underwent isolated aortocoronary bypass surgery at the Toronto General Hospital. Two hundred and ninety-nine of these patients had prolonged episodes of rest angina in the hospital which were resistant to maximal medical therapy and they therefore underwent urgent revascularization. One thousand and three patients underwent elective or semielective revascularization either because of stable angina or because their unstable symptoms had responded to medical therapy.

* Statistical Analysis System, SAS Inc., Box 8000, Cary Nc, USA

** BMDP Statistical Software, Los Angeles, CA, USA

Methods

Operative mortality was defined as a death occurring within 30 days of surgery. A perioperative myocardial infarction was diagnosed when a new Q wave developed on the electrocardiogram or if enzyme elevations or a low output symdrome developed postoperatively in patients who had a left bundle branch block or a lost R wave progression. Postoperative low output state was defined as the requirement for inotropic drugs or intraaortic balloon pump support in the intensive care unit for more than 30 minutes in order to maintain the blood pressure greater than 90 mmHg. Sixty-six, preoperative, clinical and angiographic variables were prospectively collected and analyzed for each of the outcome variables by univariate statistical analyses (chi-square statistics for discrete variables and t tests for age).* The variables which achieved statistical significance (p 0.05 by univariate analysis) were subjected to a multivariate, stepwise, logistic regression to determine the independent risk factors.**

Results

A review of the results of coronary bypass surgery between 1982 and 1983 revealed a treatment plan which was dependent primarily on the response to medical therapy. Patients who presented to the hospital with unstable angina underwent maximal medical therapy. Patients who responded completely were discharged from the hospital. Patients with an incomplete response usually underwent further investigations electively. However, patients who had an inadequate response required urgent investigation and therapy. These patients were stabilized with either intravenous nitroglycerin or the intraaortic balloon pump and underwent urgent or emergent coronary artery bypass grafting.

The overall results of coronary bypass surgery are presented in Table I. The results of the univariate analysis on operative mortality are presented in Table 2. Sex, left ventricular ejection fraction, New York Heart Association class and the presence of left main coronary stenosis all influenced the results of surgery.

The multivariate statistical analysis identified specific independent risk factors for both operative mortality and perioperative morbidity (Table 3).

Discussion

The risks of elective coronary bypass surgery have improved

markedly in recent years. However, patients who require urgent surgery because of unstable angina continue to face an increased risk of perioperative mortality and complications. In order to improve the results in this high-risk subgroup, the factors which determine outcome must be carefully identified. Because many factors influence outcome, the multivariate, logistic regression analysis was employed to determine which variable were independent predictors of outcome.

The patients undergoing elective surgery had either stable or unstable angina. If they had unstable angina, it responded to medical therapy and they underwent delayed, elective revascularization. The factors which predicted morbidity and mortality in this group included sex, ejection fraction and age. Older females with poor left ventricular function can be expected to have a higher morbidity and mortality than young males with normal ventricular function. In addition to these factors, the predictors of outcome in patients who have required urgent surgery because of unstable angina included the timing of surgery and the presence of diffuse coronary artery disease or left main coronary stenosis.

Miller and colleagues,[3] reporting the experience from Stanford, also found that sex and left ventricular function were independent predictors of outcome for coronary bypass surgery. They also found that the urgency of operation was a significant independent predictor. In the Coronary Artery Surgery Study (CASS),[2] 6,630 patients undergoing coronary bypass surgery were evaluated. They also found that age, sex, the extent of coronary artery disease and the ejection fraction were important independent predictors of outcome. The CASS report also revealed that both unstable angina and the urgency of revascularization were independent risk factors for surgery.

High-risk patients undergoing urgent revascularization can be identified by their age, sex, left ventricular function, extent of coronary artery disease, presence of prolonged episodes of rest pain which are refractory to maximal medical therapy and need for urgent revascularization. Alternative methods to improve results in these high-risk patients can be employed when the patients are identified and new approaches are developed.

Table 1

Isolated Coronary Artery Bypass Graft Surgery

Toronto General Hospital

Overall results on 1,302 pts. Operated on 1982-1983

	Stable Angina	Unstable Angina*
Operative mortality (om)	0.9%	5.0%
Perioperative myocardial infarction (PMI)	1.6%	16.7%

$p < .05$

*Unstable angina = Crescendo, rest pain or post-infarction angina

Table 2

Results of Univariate Risk Factor Analysis

	Group I Stable, elective n = 299	Group II Unstable, Urgent*
n = 1003		
Operative mortality	sex	sex
	ejection fraction	ejection fraction
	surgeon	—
	age	age
—	NYHA class	
	—	left main stenosis
Perioperative myocardial infarct	sex	—
	age	age
	—	ejection fraction
	—	surgeon
	—	myocardial protection
Low output state	sex	—
	ejection fraction	ejection fraction
	extent of CAD	extend of CAD
redo CABG	—	
	—	timing of surgery

*$p < .05$

Table 3

Results of Multivariate Risk Factor Analysis

	Group I Stable, elective n = 299	Group II Unstable, Urgent*
n = 1003		
Operative mortality	sex	sex
	ejection fraction	ejection fraction
	age	age
	—	left main stenosis
Perioperative	sex	—
—	ejection fraction	
age	age	
	—	surgeon
	—	myocardial protection
Low output state	sex	—
	ejection fraction	ejection fraction
	age	age
	extent of CAD	extend of CAD
	—	timing

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A Review of Diabetic Retinopathy

Joseph Gasser 8T5

Introduction

Diabetes mellitus is a major cause of new cases of blindness in developed countries. Medical management of diabetes has improved considerably in recent years. Patients with diabetes are now able to live long enough to develop diabetic retinopathy.

Epidemiology

The proliferative form of retinopathy (see below) is more often found in patients with insulin-dependent diabetes mellitus but a larger portion of the population has non-insulin-dependent diabetes mellitus. Both types of diabetes may develop maculopathy but patients with non-insulin-dependent diabetes mellitus are at an increased risk. The leading cause of decreased visual acuity in patients with diabetic retinopathy is macular edema.[1]

The Wisconsin Epidemiologic Study reviewed charts of approximately 10,000 diabetic patients who received primary care from July 1, 1979 to June 30, 1980. The objectives of the study were to describe the prevalence and severity of diabetic retinopathy as well as to determine relationships between risk factors, prevalence and severity.[2]

In patients who were diagnosed as having diabetes before 30 years of age the following was found: the prevalence of retinopathy varied from 17% to 97.5% in patients who had diabetes for less than 5 years and more than 15 years, respectively. For those with less than ten years duration, severity was related to longer duration, older age at exam, and increased glycosylated hemoglobin levels (one measurement only). For those with more than ten years duration, severity was related to longer duration, increased glycosylated hemoglobin levels, presence of proteinuria, higher diastolic blood pressure, and male sex.

In patients who were diagnosed as having diabetes after 30 years of age the following was found: the prevalence of retinopathy varied from 28.8% to 77.8% in patients who had diabetes for less than 5 years and more than 15 years, respectively. Severity was related to longer duration, younger age at diagnosis, increased glycosylated hemoglobulin levels, increased systolic blood pressure, use of insulin, presence of proteinuria, and small body mass.

Anatomy of the Retina

The sclera is the fibrous external coat of the eye, the choroid is the vascular middle coat of the eye, and the retina is the light-sensitive innermost coat of the eye. The outermost portion of the retina, which contains melanin responsible for decreasing scatter of light in the eye, is the pigment epithelial layer. Rods and cones are found in the photoreceptor layer (with the fovea having cones only). Nuclei of photoreceptor cells are located in the outer nuclear layer with the neural processes being in the outer plexiform layer. Nuclei and processes of cells responsible for further transmission of visual data comprise the inner nuclear and inner plexiform layers. A ganglion cell layer is found next to these. The nerve fibre layer is the innermost layer of the retina. The optic nerve is formed by the axons of the ganglion cells. (Fig. 1)

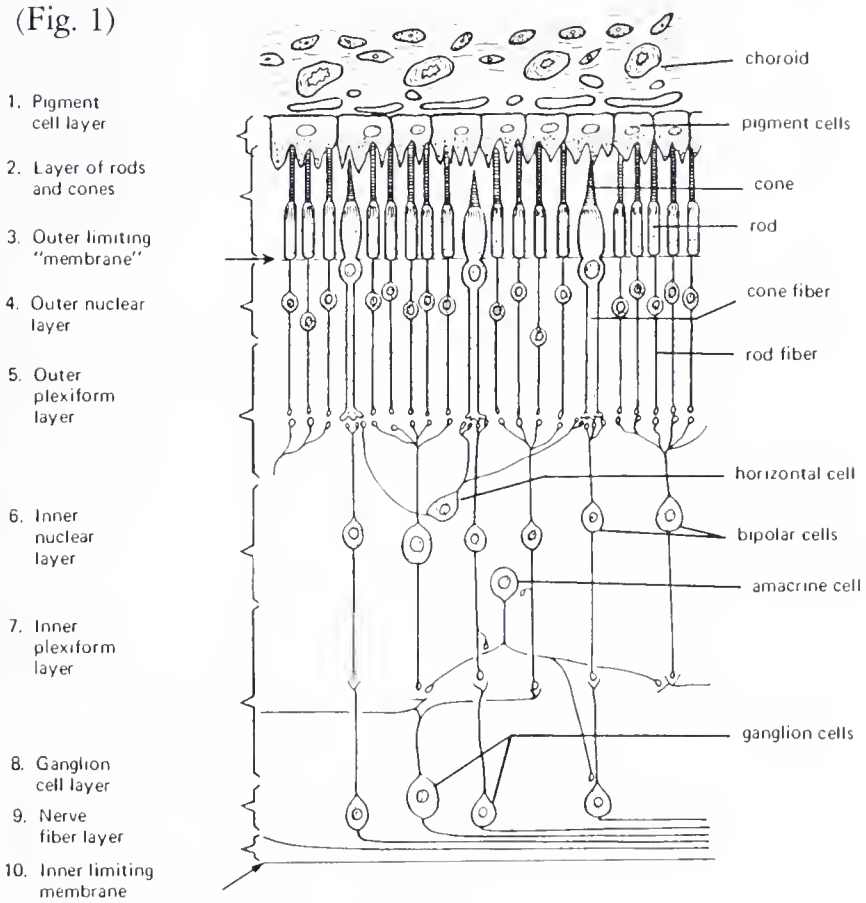

Fig. 1 Schematic representation of the cellular components of the retina.

The blood supply of the outer third of the retina comes from the choriocapillaris, this also being the only supply to the fovea. Branches of the central retinal artery supply the inner two thirds of the retina with blood vessels penetrating as deep as the outer plexiform layer.

Stages of Diabetic Retinopathy and Clinical Findings

Diabetic retinopathy is classically divided into three separate stages: background, preproliferative and proliferative. The term "background" refers to early changes that occur in retinopathy, these changes all being intraretinal. Included are microaneurysms, edema, hard exudates, hemorrhages, nerve fibre layer infarcts ("cotton wool spots"), intraretinal microvascular abnormalities (IRMA), and dilation, beading and tortuosity of veins. (Fig. 2)

"Preproliferative" refers to background retinopathy and signs of retinal ischemia which include multiple nerve fibre layer infarcts, extensive areas of IRMA and hemorrhage, extensive irregularity and beading of veins, arteriolar changes (narrowing and occlusion), and capillary drop-out (seen on fluorescein angiogram).(Fig. 3, 4)

Fig. 2 Changes of background diabetic retinopathy showing venous beading and "dot and blot" hemorrhages (arrow).

Fig 3 Fluorescein angiogram of a normal right fundus. No changes of diabetic retinopathy are seen and there is normal filling of the retinal vessels with contrast.

fibres which at this location run perpendicular to the retina. "Flame-shaped" or "splinter" hemorrhages are more superficial, at the level of the nerve fibre layer, again assuming the orientation of the nerve fibre which are parallel to the surface of the retina. These hemorrhages cannot be differentiated from hemorrhages secondary to hypertension. Large hemorrhages are seen as black splits on fluorescein angiography because they block background fluorescein.

Hard exudates look yellowish with distinct borders. These are lipoprotein deposits in the outer plexiform layer. Often they form a ring around a single leakage site (microaneurysm or capillary) assuming the so-called circinate pattern. (Fig. 7)

Cotton wool spots have indistinct borders and represent infarction of the nerve fibre layer. These spots are seen initially as areas of non-perfusion on angiogram.

"Proliferative" refers to the new growth of fibrovascular tissue. The growth is flat on the retina or elevated (pulled forward by the vitreous). It may be on or within one disc diameter of the optic disc (neovascularization of the disc–NVD) (Fig. 5) or away from the disc (neovascularization elsewhere—NVE). (Fig. 6)

The microaneurysms are seen as red spots on ophthalmoscopic exam and are often difficult to distinguish from "dot and blot" hemorrhages. They are areas of capillary dilation. Drop-out of abnormal pericytes has been noted in these regions. Because the integrity of the blood-retinal barrier has been lost it is possible for fluid and protein to leak into the surrounding retina. Edema may result if nearby vessels are unable to resorb this. Fluorescein angiograms are very useful for detecting microaneurysms which fill with contrast material and appear as white dots. Leakage can also be detected (normal intraretinal vessels do not allow leakage).(Fig. 3, 4)

Hemorrhages vary in shape depending on their site of origin. "Dot and blot" hemorrhages are deep (outer plexiform layer) in the retina, their extent being confined by the nerve

Visual loss is not common in background diabetic retinopathy unless the macula is affected. Diabetic maculopathy is a general term for a number of changes that affect the macula. These changes can be grouped into intraretinal and preretinal categories. Three components of the intraretinal type are exudation (multiple hard exudates), ischemia (large areas of non-perfusion), and edema.

Edema can further be divided into diffuse and focal forms. Focal edema is a result of leakage from microaneurysms and dilated capillaries often with a concomitant circinate pattern of hard exudates. In diffuse edema, it is relatively easier to see the retinal vessels because of diffuse loss of capillaries and widening of those capillaries which remain. Cystoid spaces may form and these can be seen by pooling of fluorescein in the late phases of angiography. The leakage is a more generalized

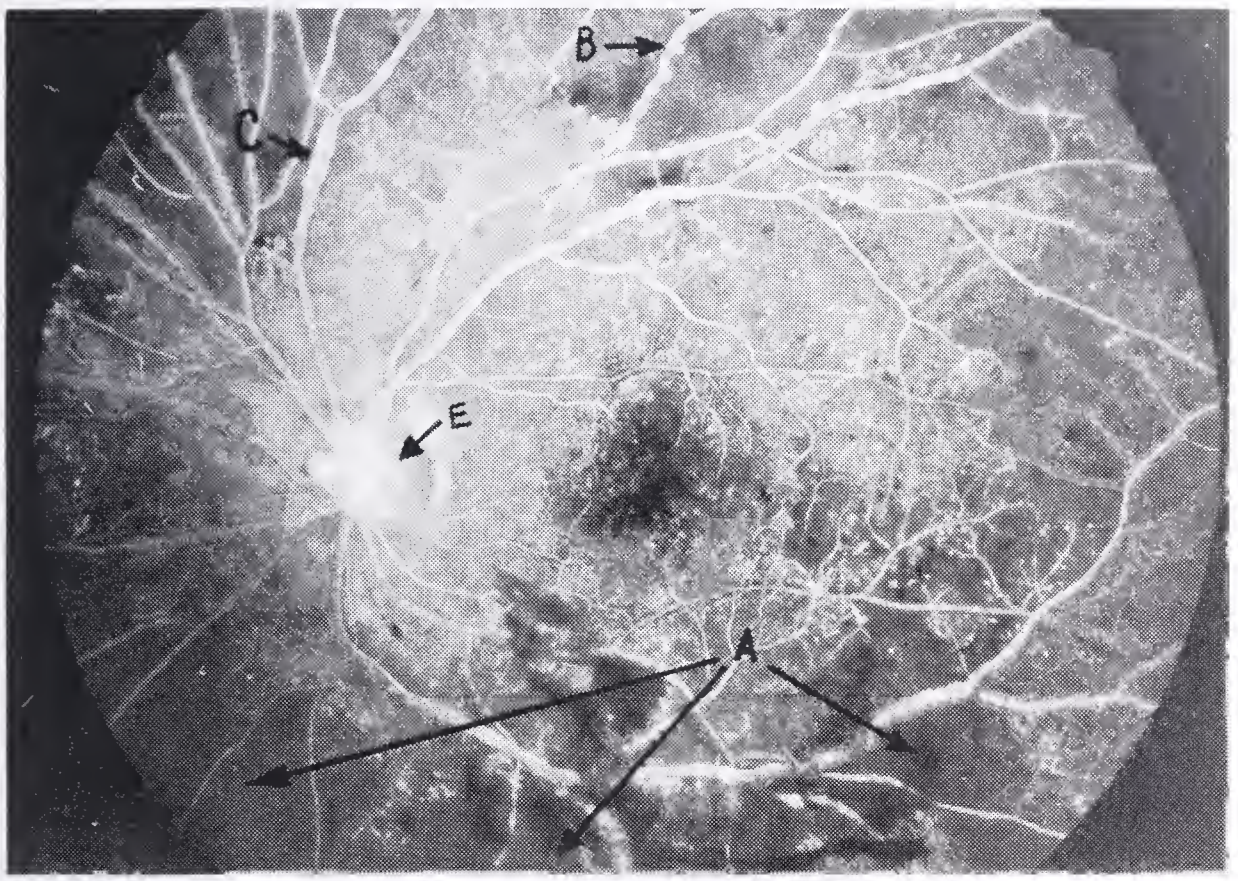

Fig 4 Fluorescein angiogram of a left fundus. Several findings of diabetic retinopathy are detected: massive areas of capillary dropout (A) venous beading (B), venous dilation (C), microaneurysms (D), neovascularization of disc (E).

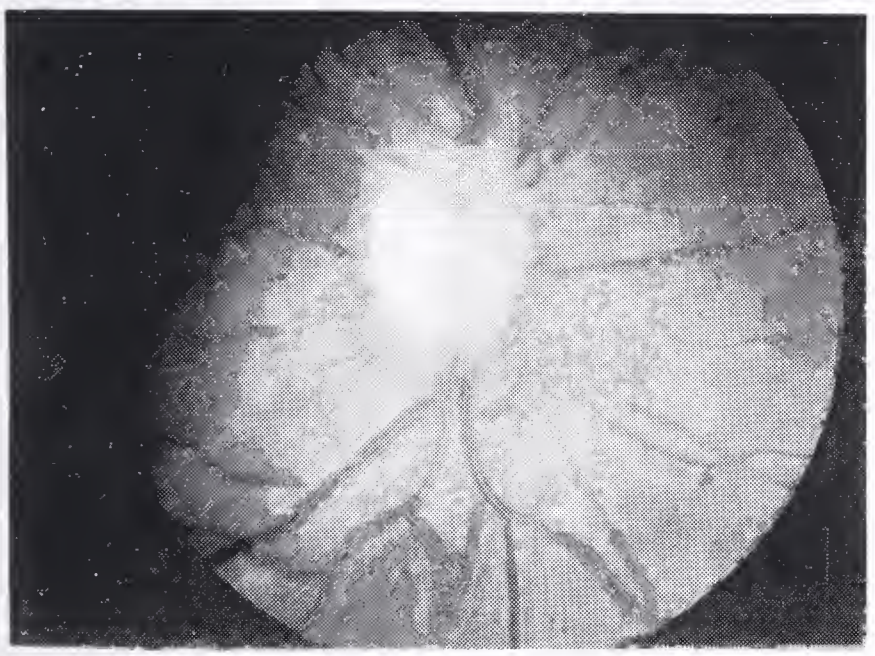

Fig. 5 Growth of fine and delicate new blood vessels on the optic disc (NVD)

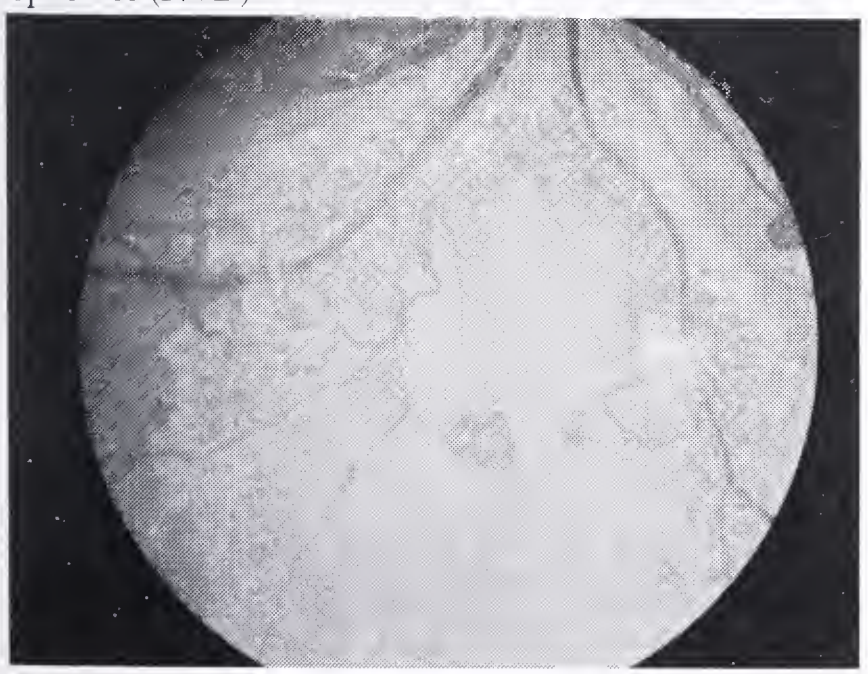

Fig. 6 Growth of tufts of new blood vessels away from the optic disc.

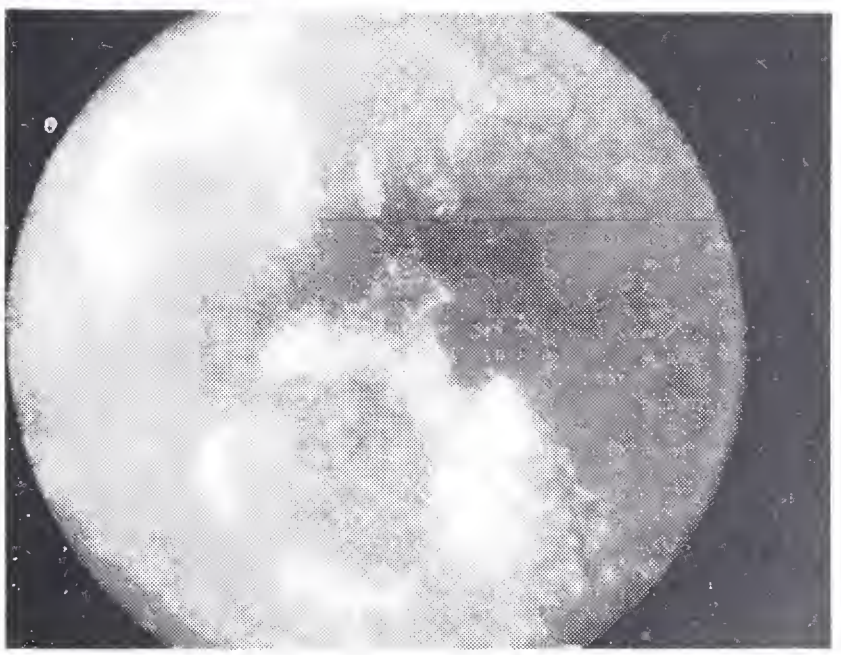

Fig. 7 Optic disc at left. Areas of circinate exudate (rings of hard exudate, each ring surrounding a single leakage site).

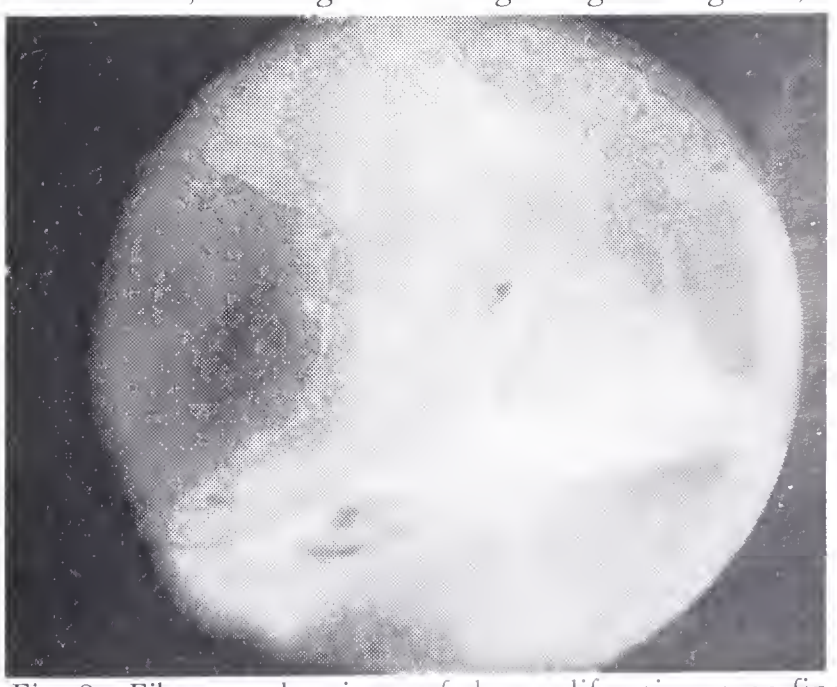

Fig. 8 Fibrovascular tissue of the proliferative stage fine blood vessels surrounded by fibrous tissue.

process than in focal edema and little or no hard exudates are seen. Poor cardiac or renal function and hypertension are factors which exacerbate diffuse edema. It is important to differentiate between the several kinds of maculopathy because they have different responses to treatment as well as different over-all prognoses.

The proliferative stage is thought to be a result of a vasogenic substance released by the ischemic retina. Three phases are detected in its development: (Fig. 8)

1. formation of delicate new blood vessels on the surface of the retina
2. proliferation of fibrous tissue
3. contraction of the fibrous tissue

The fibrovascular tissue grows forward breaking through the internal limiting membrane and forming adhesions with the vitreous. Angiography shows that the new vessels leak rapidly and extensively. Hemorrhages from these vessels are more likley to occur in phase 1) or 2). Patients are often asymptomatic until this happens. Preretinal hemorrhages (Fig. 9) take weeks to months to clear whereas vitreous hemorrhages clear after months to years, if at all.

Syneresis or shrinkage of the vitreous is a normal process that occurs with aging. Hemorrhages into the vitreous will accelerate this process. As the vitreous shrinks it pulls away from the retina. Any vitreo-retinal attachments will be stressed and this may lead to severe visual loss from either further vitreous hemorrhage or tractional retinal detachment (this may be experienced by the patient as sudden loss of vision following "flashing lights").

Prognosis for the proliferative stage depends on the location of the vessels with NVD having a worse prognosis (50% blind in 5 years).[3]

Pathogenesis of Diabetic Retinopathy

Diabetic retinopathy is characterized by disease of the blood vessels. The most important factor leading to the development of retinopathy is thought to be hypoxia of the retina. A number of conditions contribute to this hypoxia.

Blood elements have been found to be changed in patients with diabetes. Growth hormone[4] and insulin-like growth factor I levels[5] are elevated and have been postulated to affect retinopathy. Other elements found in increased levels include anti-thrombin III, factor VIII-related antigen, B-thromboglobulin, platelet factor IV, and fibrinogen.[6] Increase erythrocyte sedimentation rate and aggregation of red blood cells causing impaired blood flow have been reported.[7] Reduced red blood cell deformability[8] and increased platelet aggregation[9] have been shown.

Glycosylated hemoglobin is used as a long-term measurement of diabetes control (previous 2-3 months). An increased level of glycosylated hemoglobin and decreased levels of 2, 3-diphosphoglycerate are found[10] in patients who are not well-controlled. After glucose becomes linked to hemoglobin the oxygen-releasing potential of hemoglobin is reduced leading to hypoxia.

Fig. 9 Preretinal hemorrhage with characteristic "boat-shaped" appearance. Note that hemorrhage obscures retinal blood vessels.

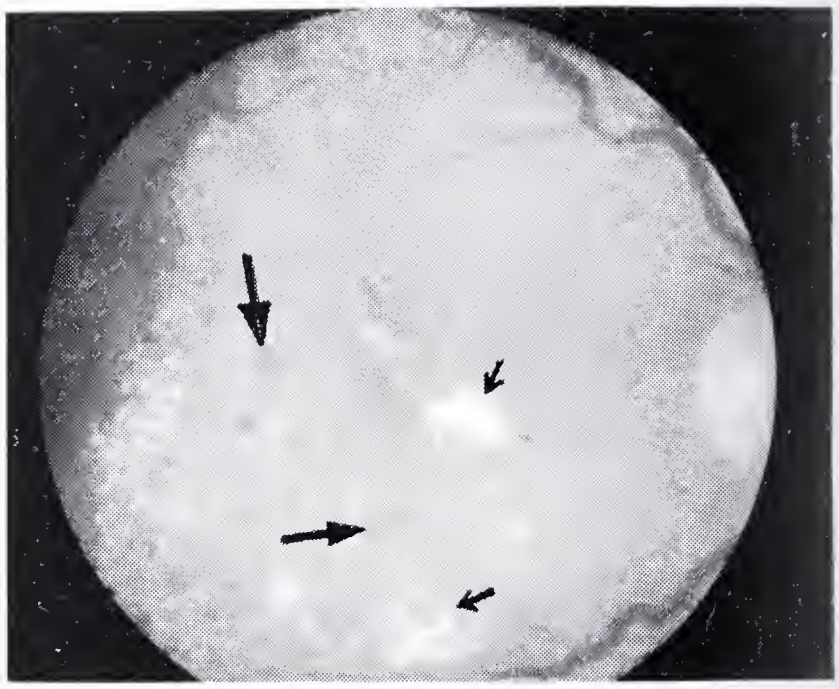

Fig. 10 Focal photocoagulation, hard exudates (small arrow); pigmented laser burns (large arrow).

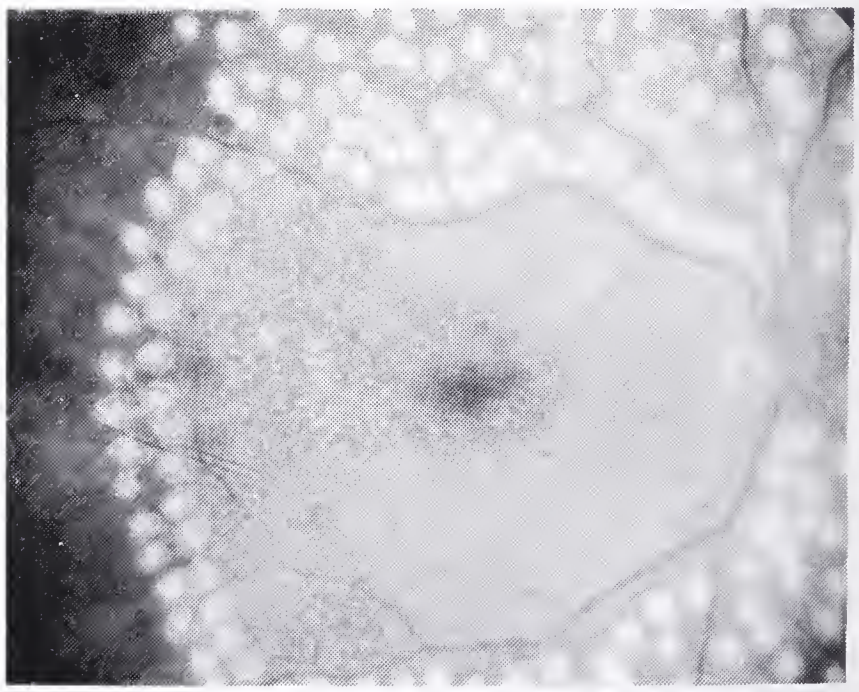

Fig. 11 Panretinal photocoagulation. Fresh (less than one hour old) laser burns along superior and inferior temporal arcades.

Photocoagulation

Photocoagulation can reduce the incidence of diabetic blindness by 65%.[22] It is the most common form of treatment for proliferative retinopathy.

Light energy is absorbed by the retina and converted to heat which occludes vessels and destroys tissue.

Photocoagulation has two major uses. In order to stop leakage from microaneurysms or abnormal capillaries these areas can be destroyed or occluded. (Fig. 10) Extensive areas of retinal hypoxia and non-perfusion, which are believed to produce a vasogenic factor that induces neovascularization, are destroyed by panretinal photocoagulation (PRP). (Fig 11)

Both xenon arc and argon laser have been used for photocoagulation but the argon laser is the most commonly used today. The following table gives characteristics of both types:

Table 1

Xenon arc	Argon laser
developed first white light	green light
absorbed by retinal pigment epithelium	absorbed by hemoglobin and retinal pigment epithelium
larger burns (> 200u)	small burns (50u-1000u) allows work close to macula
intense burns — full thickness	slit lamp used — binocular vision for operator
immobilization needed (retrobulbar anaesthesia)	no immobilization needed (high-intensity bursts, 0.1-0.2 sec)
complications more common	high focused — localized damaged

For Proliferative Retinopathy

The Diabetic Retinopathy Study Research Group (DRSRG) provided evidence through a randomized, controlled clinical trial that photocoagulation was beneficial (delay of visual loss) in the treatment of proliferative retinopathy. 1700 patients were entered into the study. Both eyes of each patient had retinopathy. One eye was randomly chosen to undergo treatment while the other eye served as a control. The effects were so significant that the protocol for the study was changed after two years so that treatment could be given to untreated eyes.

For Maculopathy

The results for maculopathy have not been as impressive as those for proliferative retinopathy but most studies have shown some benefit.[23]

The various subgroups of maculopathy show different responses to treatment. The exudative type responds best with the diffusely edematous type responding only occasionally. The ischemic form does not respond. However, prevention of neovascularization is more effective if the vessels at the macula and the ischemic periphery are treated.[24]

The method of treatment differs for the various types. In the exudative maculopathy direct treatment of the lesions is employed whereas a grid (scatter) pattern, which causes less damage, is used for edematous maculopathy.

Several hypotheses have been advanced to explain how photocoagulation works. One of these postulates that since photoreceptor cells, which consume a large amount of oxygen are destroyed thereby increasing the amount of oxygen available to the inner retinal layers and so decreasing the hypoxic stimulation for neovascularization.[12]

Complications of photocoagulation are far-outweighed by the benefits and include slight losses of visual acuity, night vision and peripheral fields, accidental foveal burn, corneal abrasions, and acute glaucoma.

Hypophysectomy

After the improvement of retinopathy following one case of postpartum pituitary infarction it was thought that some factor in the pituitary (possibly growth hormone) was important in the development of diabetic retinopathy.[25] Following this, several hundred patients were treated by hypophysectomy. Some of these patients improved. Nevertheless, the morbidity and mortality associated with this procedure has led to it being discontinued as a treatment for retinopathy.

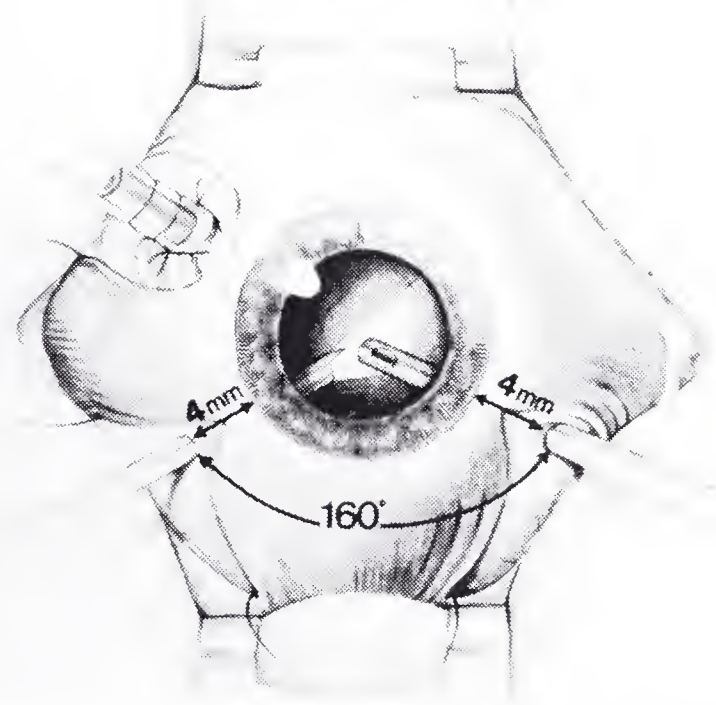

Fig. 12 Vitrectomy instruments: infusion cannula (upper left), light source (lower left), suction/cutting device (lower right).

Cryotherapy

At times, it may be difficult to photocoagulate because of difficulty in seeing the retina due to a hazy media (e.g. vitreous hemorrhage). The stimulus to neovascularization has been reported to decrease after cryotherapy.[26] Regression of neovascularization has been observed in more than 50% of treated eyes.[25]

Complications of this procedure include choroidal effusion, tractional detachment, uveitis, phthisis bulbi, or hyphema.

Vitrectomy

Vitrectomy has been performed now for more than 10 years. Better surgical equipment and improved techniques have decreased complications greatly.

Three instruments are needed. A suction/cutting device releases traction and removes membranes. A fibreoptic light

source provides illumination. An infusion cannula is used to instil fluid into the eye as tissue is removed in order to maintain intraocular pressure and prevent collapse of the eye. The instruments are inserted into the eye via the pars plana of the ciliary body (approximately 3-4mm from the limbus). (Fig 12)

There are 3 main indications for vitrectomy surgery:

1. persistent vitreous hemorrhage (often surgery is delayed for 6-12 months as the hemorrhage may resolve spontaneously).
2. tractional retinal detachment with retinal holes
3. tractional macular detachment

With vitrectomy surgery it is possible to reattach portion of torn retina, relieve traction, strip membranes, and clear persistent hemorrhage. Fig 13, 14

In the early 1970's clear lenses were often removed. It was found that this resulted in an increased incidence of rubeosis iridis and neovascular glaucoma. Lenses are now removed only if absolutely necessary (cataract; to allow better visualization).

Complications of vitrectomy include iatrogenic retinal tears (reattached by a scleral buckle or air/fluid exchange), neovascular glaucoma, and postoperative hemorrhage. The incidence of postoperative hemorrhage has been decreased by the use of endodiathermy before cutting fibrovascular tissue and at the end of the surgery.[28]

It has been proposed that if, after photocoagulation, the vascular component of fibrovascular proliferation regresses but firm adhesions between the vitreous and retinal surface are still evident, vitrectomy should be used to separate these adhesions with the major goal being prevention of tractional retinal detachment and preservation of good vision.[29] Further flat neovascularization is rare and elevated neovascularization has not been observed to follow.[30]

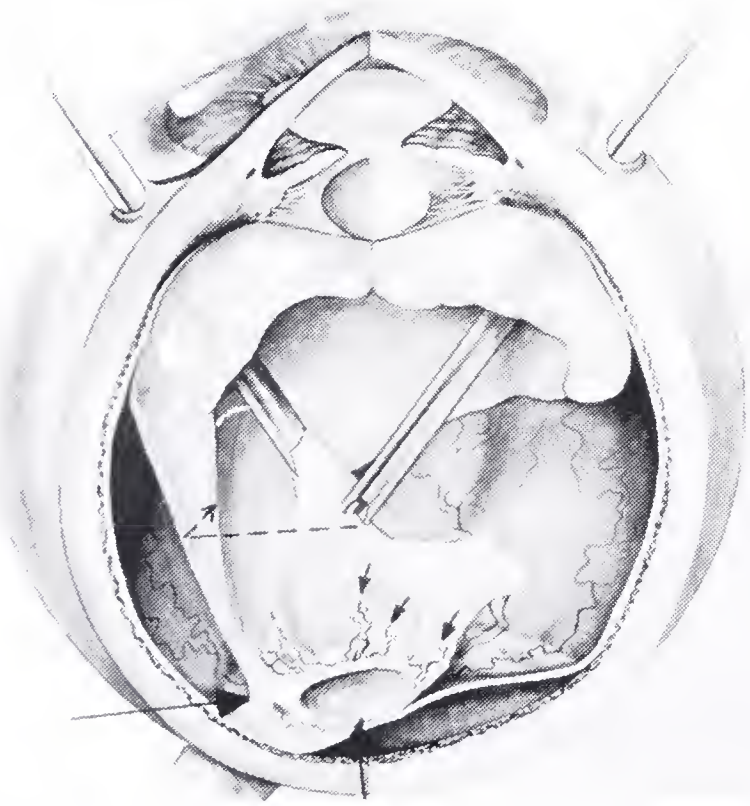

Fig. 13 Vitrectomy. After removal of vitreous gel traction exerted by detached posterior vitreous surface is relieved by cutting (broken arrow). The remaining vitreoretinal attachments are then resected (large arrows). Note the retinal detachment at the posterior pole and fine retinal blood vessels forming adhesions with the vitreous (small arrows).

Current Research

Sorbinil (an aldose reductase inhibitor) is being evaluated for use in prevention or delay of diabetic retinopathy. The three year, double blind, placebo-controlled study will finish in July 1986.

The Early Treatment Diabetic Retinopathy Study will have approximately 2000 patients. The efficacy of photocoagulation and aspirin (anti-platelet effects) are to be analyzed in patients with macular edema.

The Diabetic Retinopathy Vitrectomy Study is evaluating the results of vitrectomies done at various stages of disease.

Elevated blood glucose levels result in increased glucose within cells being metabolized by aldose reductase which produces sorbitol. This sugar alcohol does not cross membranes readily and so accumulates within the cell. The increase in osmotic pressure eventually results in cellular edema. This may be the mechanism for loss of pericytes[11] one of whose roles is support for capillaries. The break in the blood-retinal barrier produces edema and hard exudates.

The hypoxic retina is believed to release a vasogenic factor which is responsible for neovascularization.[12]

Fig. 14 Post-vitrectomy. All traction is relieved and the retina has been reattached.

Treatment

Animal studies have shown that excellent control of blood glucose levels can prevent microvascular complications.[13] However, in humans, optimal control has not been shown to prevent retinopathy.

In the past it was not possible to assess long-term control of glucose. Nevertheless, newer technology might overcome this problem. Continuous subcutaneous insulin infusion (CSII), made possible by portable insulin pumps, delivers a more physiologic dose of insulin than can be delivered by conventional injection methods.[14] Glycosylated hemoglobin measurements are used for long-term indications of diabetic control. Reliable self-monitoring is obtainable with glucose oxidase strips and reflectance meters.

Some anecdotal reports described how a reversal of retinopathy was achieved using CSII to strictly control blood glucose.

Several studies later indicated that the CSII actually produced a progression of the retinopathy[17] and it was suggested that very tight control after an extended period of poor control was harmful.[18]

The mechanism for the deterioration is not known. Reduced retinal blood flow is one possibility. An elevation of glomerular filtration rate is seen with poor control.[19] With normalization of glucose levels the glomerular filtration rate is reduced[20] and it is felt that a similar mechanism may occur in the retina leading to further deterioration. Chronic hypoglycemia was also considered but was not noted in any of the patients.[17]

One study observed effects of CSII only on patients with preproliferative and proliferative retinopathy. It was postulated that in these conditions a hypoxic stimulus was already set up by extensive areas of non-perfusion and that CSII was not able to overcome this.[17] However, a benefit for background retinopathy was not ruled out. Studies are presently being done to see if there is indeed an indication for CSII in mild retinopathy.

A "transient proliferative retinopathy" has been reported in a patient with mild retinopathy. Progression of the retinopathy was noted in the first three months of CSII with complete regression seen after four more months of CSII.[21]

There is potentially a point of no return in diabetic retinopathy beyond which CSII is harmful rather than beneficial.

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Radial Keratotomy — The Surgical Management of Myopia

Dara Hoffman, 8T6

Eye glasses and contact lenses are the standard, uncomplicated methods of treating myopia. Many individuals have long desired to rid themselves of corrective lenses and the associated stigma of "four eyes". Recently, surgical correction of myopia by Radial Keratotomy has attracted the attention of the public, and created a controversy among eye surgeons in the United States and Canada. This paper will explain the technique and review the recent literature regarding results and sequelae.

Introduction

The concept of surgically changing the refractive power of the cornea dates back to the 1800's. It was at this time that an advertisement appeared in which Dr. J. Ball promoted a spring-loaded eye cup which he claimed would flatten the cornea through the closed eye.[2,8] Scientific articles were first published in 1869 regarding the surgical correction of astigmatism.[4] As surgical techniques improved, refractive surgery progressed significantly, and at the present time, one procedure is being actively investigated and performed clinically: Radial Keratotomy (R.K.). This operation has been performed on over 35,000 Americans in the U.S. since 1979.[20] The question of whether the risk/benefit ratio is low enough for R.K. to gain general acceptance remains to be answered.

The cornea performs the majority of the refraction (bending and focusing) of light entering the eye. The lens of the eye also refracts light, but to a smaller extent. A refractive error is a defect that prevents light rays from being brought to focus on the retina. The unit of measurement of refractive error is the diopter. Myopia (near-sightedness) is a condition in which the eye has too much refractive power for its relative longer length. Thus the point of the image of a distant object is focused anterior to the retina. A negative (concave) lens is used to correct myopia, hence the refractive error is expressed in negative diopters.[26] R.K. aims to reduce refractive power by flattening the corneal surface.[25]

Technique

Radial Keratotomy is a twenty minute procedure in which eight or sixteen radial incisions are made in the external surface of the cornea. Preoperatively, the patient is assessed for visual acuity, refractive error, and central corneal curvature (keratometry). The cornea ia anaesthetized with topical drops. The optical zone, a small area surrounding the visual axis of the cornea, is outlined on the corneal epithelium. A surgical diamond blade is inserted into the cornea at the border of the optical zone. Eight or sixteen radial incisions (90 — 100% of central corneal thickness) are made out to the limbus.[23,25] (Fig. 1) The incisions weaken the structure of the peripheral corneal stroma, the intraocular pressure then causes a bowing forward of the peripheral cornea, increasing peripheral curvature and secondarily flattening the central region.[22, 25] The operation may be perform on an out-patient basis.[16]

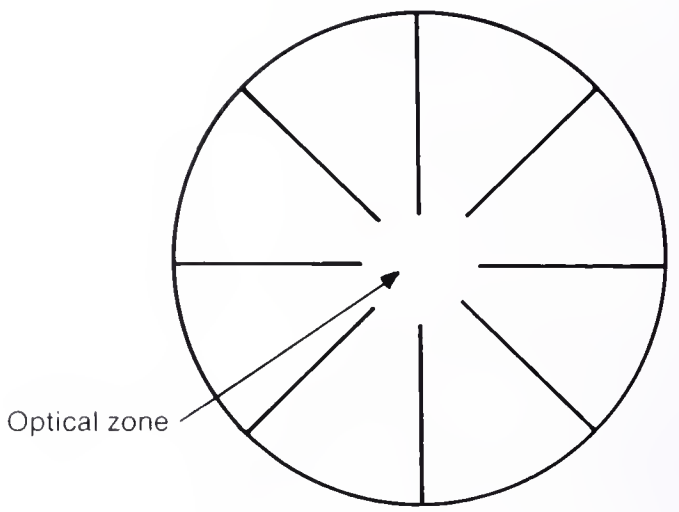

Fig 1 Radial Keratotomy. Cornea with eight symmetrical radial incisions.

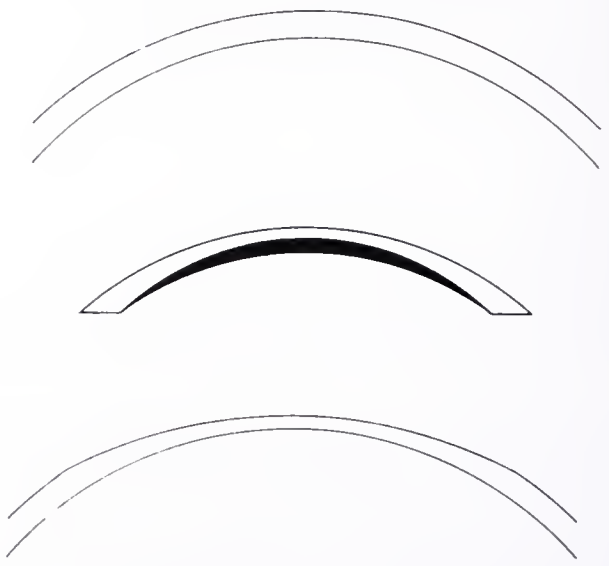

Fig 2 Effect of Keratomileusis on the cornea: a) Cornea prior to surgery b) Keratectomy; resected stroma (black) c) Cornea following surgery.

A variant of the procedure used today was first performed between 1939 and 1953 by Sato.[13,28] Akiyama followed 177 of 281 eyes which Sato had operated on.[13,28] Although he found an average decrease in refraction of 3.10 diopters, many patients developed corneal edema, and thus Sato discontinued the operation. Sato used incisions in both the epithelial and endothelial corneal surfaces. Some surgeons have assumed that the endothelial cuts caused the corneal edema (the endothelium plays an important role in corneal fluid balance). Endothelial cuts have been eliminated from procedures used today.[13,28] In 1979, interest in refractive surgery was renewed when Fyodorov presented the first report on radial keratotomy in western literature. Fifty radial keratotomies were being performed weekly in a Moscow institute. The Russians claimed dramatic reduction in myopia with excellent postoperative unaided visual acuity.[23] These results were subsequently reported by the lay press worldwide. Many patients expressed interest in undergoing R.K. Surgeons began performing the procedure in the United States in 1979, and have since operated on over 35,000 eyes.[20]

Results

Numerous studies have been and are currently being carried out to assess the effectiveness and potential complications of Radial Keratotomy. Results of independent studies have shown the procedure to be effective in reducing myopic refractive error (Table 1). The potential of obtaining an uncorrected visual acuity of 20/40 (legal driving limit) or better is 85—90% for the patient who is in the myopic range of 1 to 4 diopter, with +1.50 or less of astigmatism. This potential is decreased to 60% as the degree of myopia increases to the 4 to 6 diopter range.[20] However, poor predictability and variable results remain as major problems.[13] The range of correction is limited to 1 to 6 diopters. Thus for patients with degrees of myopia greater than 6 diopters, R.K. may only reduce their prescription, decreasing the thickness of corrective lenses. The final result is achieved at approximately 4—6 months postoperatively.[20]

The long term sequelae of radial keratotomy are not known. The rate of short term complications varies among studies, but the overall complication rate is low (one year follow-up). Intraoperatively, corneal perforation occurs in 10—20%, generally with no sequelae. Epithelial defect or ingrowth, and stromal edema are early postoperative complications. Late postoperative sequelae include fluctuating visual acuity, glare, photophobia, endothelial cell loss, overcorrection, regression, corneal iron lines, corneal neovascularization, excessive scarring, corneal ulcer, stromal keratitis, epithelial inclusion cysts, iritis, and cataracts. The major visual complications of fluctuating vision, glare, and photophobia tend to resolve by the sixth postoperative month. Patient satisfaction rate has been reported to be approximately 90% in the United States.[8,9,11,14,18,19,20,22,24]

The National Eye Institute in the United States is currently sponsoring a five-year prospective multicenter clinical trial to evalute the effectiveness and complications of Radial Keratotomy. This study, Prospective Evaluation of Radial Keratotomy (PERK) began in 1980. The initial report discussed the psychosocial reasons for which patients sought the procedure. The majority of patients desired an improvement in uncorrected visual acuity to achieve career goals, however many individuals simply wished to stop wearing corrective lenses. The results of the PERK study will continue to be published throughout the course of the investigations. Some opthalmologists feel that R.K. should be considered investigational until this study is completed.[3,7,27] The Canadian Society of Opthalmologists views R.K. as an experimental technique. The operations was recently performed (January 16, 1985) by Dr. Howard Gimbel on the Canadian television progrom, "Market Place". One other Canadian surgeon, Dr. Marvin Kwitko, has performed R.K. in Montreal, Quebec.[16]

Many people dislike wearing corrective lenses. In the near future, radial keratotomy may offer hope for the correction of myopia. Between ten and twenty percent of the population would be eligble candidates for this procedure. Therefore, a significant incidence of complications could lead to extensive disability.[12] The evidence thus far (short term follow-up) generally indicates the procedure to be safe and effective, but predictability remains a problem.[9] Radial keratotomy raises questions regarding the indications for invasive ocular surgery; its benefits primarily psychosocial, while its risks remain to be defined.

Table I Results of Radial Keratotomy

Source, Year of Results	Number of Eyes	No. Mos. Post-op Assessment Performed*	No. of Incisions	Degree of Pre-op Myopia (diopters)**	Post-op Change in Refraction (diopters)**	% Attaining unaided V.A. 20/40 or better**
Bores et al,[4] 1981						
Group 1	97	12	16	Range -2.00 to	1.74	28
Group 2	303	12	16	-11.00	4.23	61
Hoffer et al,[10]	52	Mean 24.7	16	-5.20	3.85	50
1983	63	Mean 9.4	8	-3.84	2.85	65
Arrowsmith et al,[2]1983	156	6	8 or 16	-5.00	4.8	73
Nirankari et al,[17] 1983	58	19	8 or 16	-1.93	2.7	48
Deitz et al,[6] 1984	269	12	8	-4.8	5.0	83
Singh et al,[21] 1984	1200	6	12 or 16	Range -1.00 to -5.50 or above	1.9	55

*Absolute, unless specified.
** Mean, unless specified.

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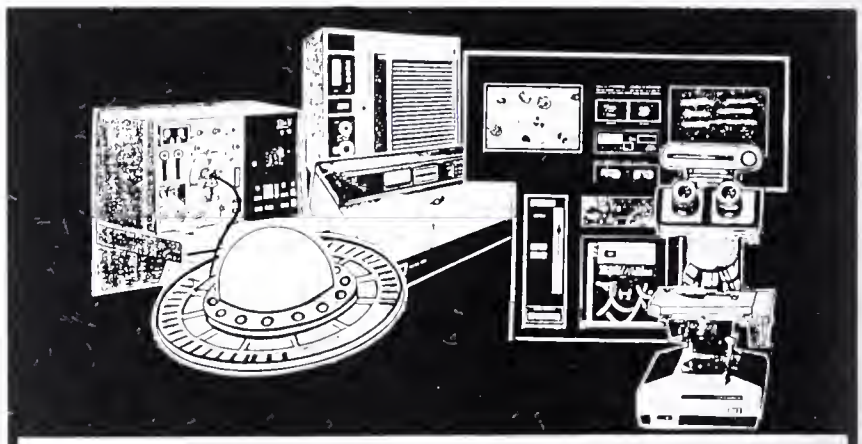

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Pain Perception: An Overview

Linda Harvey, B Sc, MSc 8T5

Many of our future patients will be experiencing pain. All of us have experienced pain ourselves. Pain can be either a signal that something wrong is happening to the body or, as in certain nerve injuries or chronic conditions, it can be an entity in itself to be treated. The intent of this article is to provide a rapid overview of what is currently known about pain pathways and pain perception in health and injury, and to take a quick look at some of the work in progress in this area.

First, let us take a look at the pain pathways. Two main types of nerve fibres carry most pain signals from peripheral receptors to the central nervous system. C-fibres are small, unmyelinated, slowly conducting fibres which are responsible for conducting crude touch, temperature, deep pressure, tickle, itch and poorly localized "burning" pain. Most visceral pain travels along these fibres. C-fibre receptors are almost entirely free nerve endings.

A-delta fibres are large, myelinated, rapidly-conducting fibres which carry the sensations of light touch, position and well localized "pricking" pain. The receptors associated with these fibres are also largely free nerve endings in the skin and other tissues.

In addition to A-delta there are also A-beta fibres, even larger and faster than the A-delta fibres. These have an important sensory function in the detection of light touch, vibration and joint position sense, etc., but do not carry pain messages as a rule. Their receptors are often complex structures such as Pacinian corpuscles, Ruffini's end organs, Merkel's discs, etc.

Pain messages travelling along the A-delta and C-fibres are conducted into the dorsal horn of the spinal cord (Figure 1). There, various intricate sorts of connections are made between incoming neurons, spinal cord neurons (interneurons), ascending tracts carrying messages to the brain and descending tracts carrying modulating signals from the brain.

Two major systems carry pain messages up the spinal cord; the dorsal columns and the spinothalamic tracts. (Figure 1) The former is a highly specially organized rapidly conducting system which principally carries information from the A-delta and A-beta fibres and subserves light touch, vibration, position sense and well localized "pricking" pain. These signals are conducted largely unprocessed up into the central nervous system. The other system, the spinothalmic tract, is the more primitive of the two. It is more slowly conducting, has relatively poor spatial organization and is subject to a high degree of modulation at several points along its path. It carries poorly localized "burning" pain, visceral pain, crude touch, temperature, tickle and itch.

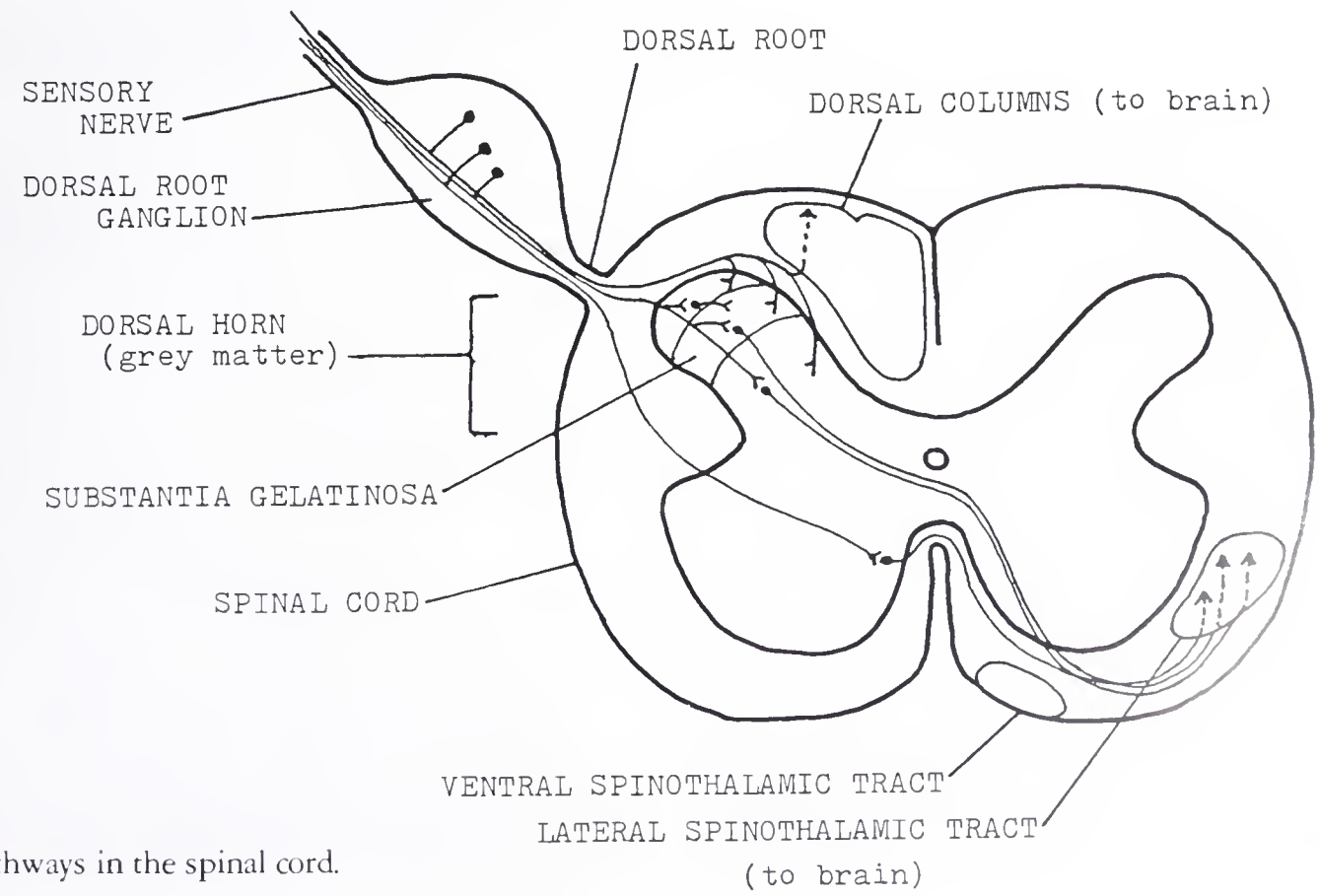

Fig 1 Pain pathways in the spinal cord.

Both of these systems conduct their impulses up through the brain stem, into the thalamus, and thence to the sensory and association areas of the cortex where conscious appreciation is thought to take place.

As mentioned, incoming signals are subject to various modulatory influences as they enter and ascend the cord. One of the most important of these modulators is the opiate system which acts at several points along the pain pathway. The discovery that there were receptors for opiate drugs in the central nervous system led to a diligent search for the endogenous compounds which activated these receptors. Subsequently the peptides met and leu - enkephalin, beta endorphin and more recently the dynorphins,[32] were found to fill this role and 3 subtypes of opiate receptors were distinguished, each with its own pharmacological properties. The opiate system is very complex and not yet fully understood. However, cell bodies and terminals of opiate-containing neurons have been found in both the dorsal horn of the spinal cord [14,34] and in many areas of the central nervous system, including the midline nuclei of the brain stem, the periventricular gray, the locus ceruleus and others.[14, 32, 23] (Figure 2). In the spinal cord, enkephalin containing cell bodies have been found in all layers of the dorsal horn and are thought to act as interneurons.[12,32] From the brain stem nuclei, descending processes of opiate containing neurons travel in the dorso-lateral funiculus of the spinal cord to the dorsal horn where they are thought to impinge on incoming pain fibres. (Figure 3) Receptors for opiate peptides are present on sensory nerve fibres of the dorsal horn, particularly in the substantia gelatinosa, but no anatomical evidence has been forthcoming that opiate containing nerve terminals are associated with these receptors.[32] However, morphine injected into the opiate containing brain stem nuclei will cause analgesia while opiate antagonists injected into the same areas block the effects of systemically injected morphine. Also, electrical stimulation of these areas reduces activity in some dorsal horn neurons and this effect is blocked by section of the dorsolateral funiculus.

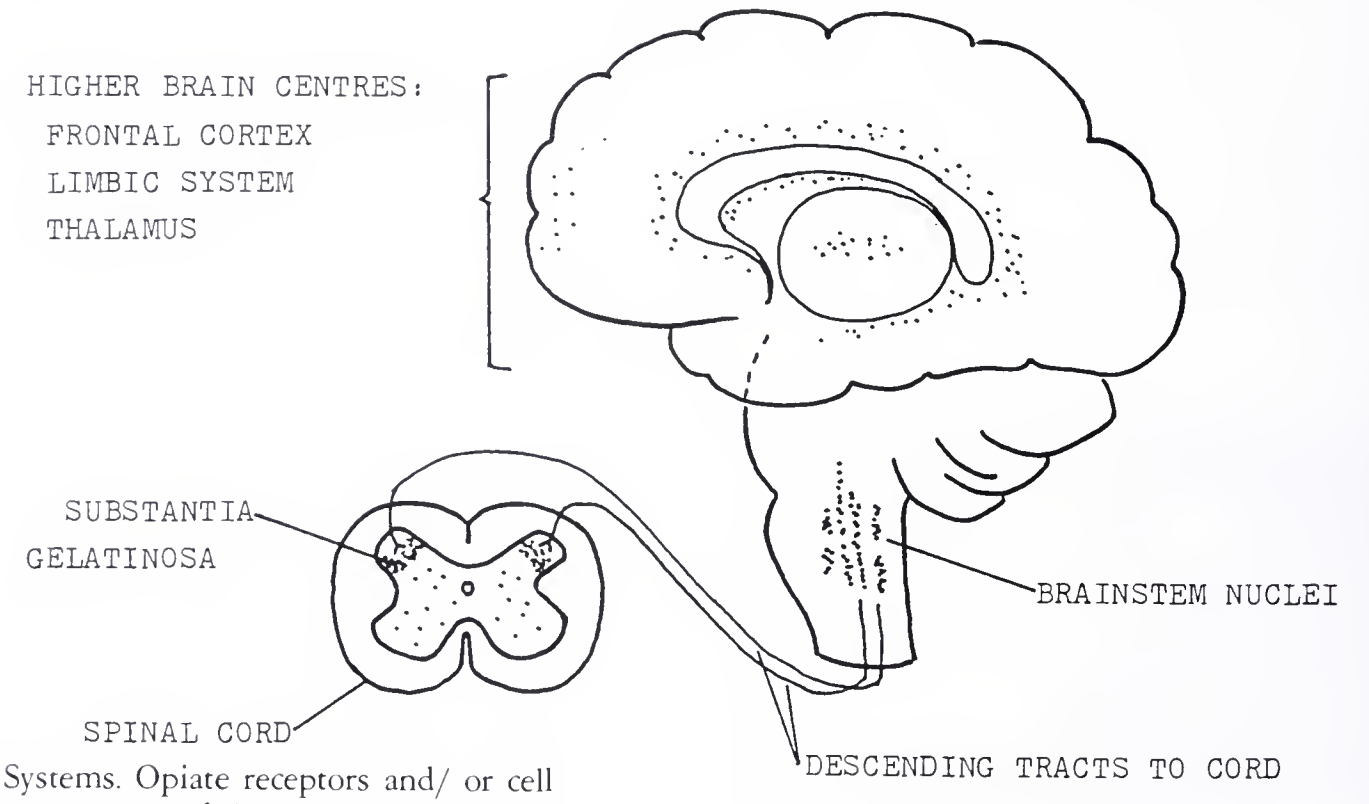

Fig 2 The Opiate Systems. Opiate receptors and/ or cell bodies are found in many parts of the brain. Of particular importance to pain perception are those in the brainstem nuclei connected via descending tracts to the spinal cord.

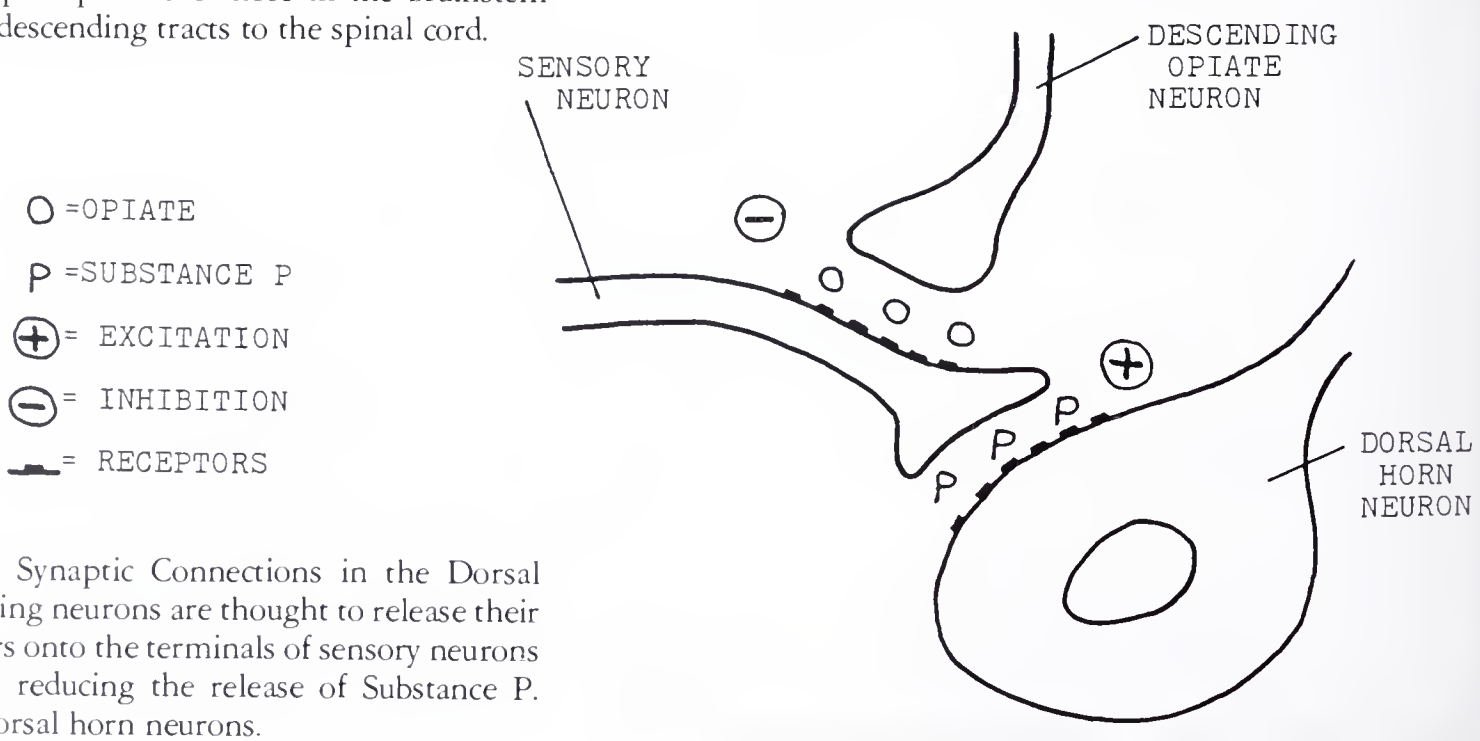

Fig 3 Hypothetical Synaptic Connections in the Dorsal Horn. Opiate containing neurons are thought to release their inhibitory transmitters onto the terminals of sensory neurons carrying pain signals reducing the release of Substance P. Substance P excites dorsal horn neurons.

The opiate system tends to have a dampening influence on incoming and ascending pain signals and hence its analgesic effect. The pain relieving properties of drugs such as morphine and codeine are thought to be due to their ability to enhance activity in these pathways.

In addition to the endogenous opiates, several other chemical substances are known to have an influence on pain perception. Some of these have been localized to discrete neuron systems, others have not. The neurotransmitter serotonin has been shown to have a facilitatory effect on descending opiate paths,[1, 34] and thus to enhance analgesic activity. This may explain the effectiveness of the antidepressant drugs, which enhance serotonergic activity, in ameliorating chronic pain in some patients. Norepinephrine appears to have a more complex action[34] - it may inhibit pain in some descending pathways[34] but at the sensory receptor level, particularly in injury, it seems to enhance it.[29, 34, 34] In the dorsal horn the peptide substance P is thought to be the transmitter released by incoming sensory nerves.[12] Its release is inhibited by opiate substances acting presynaptically on the axon terminal. (Fig. 3) In addition, there are other peptides in the dorsal horn including neurotensin, somatostatin and cholecystokinin[12] which are thought to be involved in pain regulation although their exact roles have not been worked out. Very important from a clinical point of view are the substances released by inflamed, ischemic or otherwise damaged tissues including bradykinin, histamine, serotonin and the prostaglandins.[34,35] These substances tend to activate nerve endings and thus to increase the number of pain signals entering the central nervous system. This is one of the mechanisms underlying "tenderness" - the experience of pain with a stimulus which would not ordinarily be felt as painful. Drugs such as ASA and the non steroidal anti-inflammatory drugs which act to inhibit prostaglandin synthesis act best on this type of pain, as well as having other effect on inflamed tissue.

The "Gate Control Theory" was developed by Melzak and Wall in 1965[20] in an attempt to explain some of the physiological and clinical data which was available to them at that time. According to their formulation, there is a tonic input from both large non pain fibres (A-beta and some A-delta) and small pain fibres (A-delta and C) to the dorsal horn of the spinal cord and that this acts to keep a gating mechanism in the dorsal horn partly open. Input from non pain fibres was thought to push the gate closed, input from pain fibres to open it. Thus, a peripheral stimulus of increasing intensity would be felt first as touch or another sensation and would actually inhibit pain transmission, then would become painful as more small fibres were recruited. In addition, since large fibres adapt and small fibres do not, a prolonged stimulus would tend to become painful over time as the "gate closing" fibres gradually shut off, while the "gate opening" ones persisted.

The publication of this theory sparked a great deal of controversy and much research activity in this area. Subsequent studies have supported some aspects of this formulation but not others. On the whole, the picture has turned out to be very much more complex than either Melzak or Wall predicted, as is often the case in physiological studies. It has been possible to demonstrate inhibitory activity by large fibres at the level of the dorsal horn of the spinal cord as predicted,[34,35] but small fibres also appear to have an inhibitory effect.[35] Large fibres do adapt more rapidly than small fibres but the significance of this in terms of pain perception is still being examined.

Clinically, there is some evidence that large fibre activity does inhibit pain transmission. This forms the basis of such manoeuvres as rubbing or holding the site of an injury, "effleurage" or lightly touching the abdomen of a woman in labour to reduce labour pains and may be one of the mechanisms behind the effectiveness of trans-cutaneous electrical nerve stimulation (TENS) and acupuncture in relieving pain.[35]

So far we have been considering the conduction of pain signals from injured tissues through normal nerves. When peripheral nerves are crushed, avulsed or severed, either partly, or completely, changes in conduction patterns along these nerves may occur which are of paramount importance in assessing and treating the pain syndromes which may arise as the result of these injuries. It is not unusual for these "deafferentation" injuries to give rise to severe pain or hyperesthesia (the perception of mild stimuli as intense and often painful) in the distribution of the damaged nerve, which persist even though the nerve has been completely severed or has had ample time to regenerate, adapt, etc. Such painful sequelae do not occur in every patient but when they do, they are notoriously resistant to treatment, even by opiate analgesia or surgery proximal to the injury.

Among the mechanisms by which the generation and conduction of nerve impulses may be altered in peripheral nerve injuries are the following:[19, 21, 22, 29, 34]

1. Axon receptor mismatch: Regenerating axon sprouts, although showing a strong preference for their own type of receptor, may, on occasion, link up inappropriately giving rise to confusing signals on stimulation. Similarly, sprouting axons can reinnervate territory they did not originally serve.
2. Damage to nerve fibres along their course may make them more susceptible to ischemia or deformation. Both of these processes alter the cell membrane properties and can give rise to aberrant signals or altered conduction.
3. Adhesions and scar tissue around the nerve can contribute to ischemia and deformation of the nerve.
4. Degenerating or regenerating axons also have abnormal cell membrane properties and tend to be hyperexcitable. They can give rise to aberrant signals either spontaneously or by "auto excitation" immeditely after a signal has passed.
5. Electrical "cross-talk" can occur between damaged neurons denuded of their myelin or Schwann cell sheaths, as can unusual structural connections. Often stable patterns abnormal conduction can be set up in this manner.
6. Neuromas may form, either along a damaged nerve or at the stump of a severed one. These consist of tangles of regenerating axon sprouts unable for various reasons to find their way to an appropriate peripheral terminus. These have similar properties to the sprouting axons discussed above and are often spontaneously discharging, pressure sensitive and may show a prolonged after-discharge after stimulation. They can be extremely painful.

In addition to the changes occurring locally at or near the site of injury, damage to a peripheral nerve often gives rise to adjustments more proximally and within the central nervous system. The dorsal root ganglion of the nerve and the dorsal horn of the spinal cord are typically involved.[13, 19, 29, 30, 31, 34]

After section, or partial section of a peripheral nerve, there is an increase in activity in the dorsal root ganglion cells, possibly due to disinhibition. There is a loss of several inhibitory phenomena in the spinal cord including the inhibition of C-fibres by A-fibre activity.[30] There is a shift in receptive fields of denervated dorsal horn cells to include inputs from intact sensory fibres. Later there may be degeneration of both dorsal root ganglion cells and their inputs to the cord.

In dorsal root section or avulsion injuries the changes are more dramatic and they include rapid degeneration of terminals, reorganization of the surviving cells into abnormal configurations and possibly denervation supersensitivity of partially deafferented cells, as well as sprouting of surviving cells to try to reestablish lost connections.[30] Later, gliosis, or scarring may distort cells.[13]

Once these changes happen, they are not reversible, and the sensory phenomena they give rise to are extremely difficult to treat. Even manipulations more proximally in the central nervous system such as thalamic lesioning are not always helpful.

In addition to injuries, there are a number of degenerative diseases of the nervous system which can give rise to abnormal sensory signals, including pain. These each have their own unique mechanism and include multiple sclerosis, diabetic neuropathy, amyloidosis, Fabry's disease, Tangier's disease and many others.[6, 26, 34]

The perception of pain is by its nature very subjective, a private experience. It can be communicated by verbal report - by comparison to sensory experiences known to all, or by exclamation or epithet. It can be revealed in behaviour - holding a body part, doubling over, limping; or by physical signs - muscle tension, blood pressure, heart rate, sweating. But all of these are indirect. Do we really know what that person is experiencing?

Pain behaviour and possibly some aspects of pain perception are influenced by culture, learning and environment. They are also influenced by anxiety, depression and hypochondriasis, secondary to the injury or to other factors such as compensation proceedings. Self-report of pain is also subject to these biases.

It has been the subject of much recent research to try to determine how sensory signals are translated into the experience of pain, whether there are physiological correlates which accurately reflect conscious pain perception and why there are such wide interindividual variations in the amount of pain reported from apparently similar injuries. We have seen how the nervous system can adjust to injury to produce abnormal signals. Now we will take a look at how signals, normal or abnormal, are translated into pain.

It is generally agreed that the pain threshold, defined as the minimum intensity at which the stimulus becomes reported as painful exactly 50% of the time, is relatively constant for a given type of stimulus.[9] It does not vary greatly between individuals or across cultures. It is lowered by inflammation in the stimulated tissues and raised by local anesthetics, centrally acting analgesics, and certain lesions to the nervous system, all of which interfere in some way with the transmission of pain signals. However, it has been noted that certain variables, such as attention, concurrent stimulation, social conditioning, anxiety, expectation and suggestion, etc., tend to affect reported pain in a given stimulus situation. In an attempt to resolve this apparent discrepancy, sensory decision theory (SDT), also known as stimulus detection theory, was devised.[5,10,33] This is a method of data analysis which purports to separate purely sensory phenomena from the effects of expectation, interpretation and the decision-making process concerning whether to report a stimulus as painful. According to this formulation, the traditional pain threshold measurement is divided into two components, each derived through a rather complex statistical analysis of stimulus and response pairs. The quantity d' or discriminability reflects the subject's ability to perceive a signal and distinguish it accurately from lower or higher intensity signals. A low d' results when there is background noise or confusing concurrent input, as in distraction or suggestion, or when neural activity is attenuated in the sensory system, as after certain analgesics, or in the case of fatigue or disinterest. A low d' does not mean that pain is not felt but that the discrimination of signals is faulty. The second value determined by this method is beta, or the response criteria, which describes the cut-off point at which the subject decides to report the stimulus as painful. It may be decreased by anxiety or secondary gain and increased by stoicism, denial and centrally acting analgesics.[33]

The interpretation of STD analyses is still a subject of much controversy, particulary with regard to the effects of analgesics and motivational factors. The final word on the influence of various conditions on experienced and reported pain is still far from in.

Several recent studies have addressed the issue of the correlation between sensory signals conducted through various parts of the nervous system and reported pain. These have yielded some valuable insights into sensory information processing and may form the basis for a much deeper understanding of the mechanism of pain.

A series of studies by Torebjork and co-workers[16,27] examined activity in single C-fibres associated with single receptors responsive to heat, mechanical deformation and pain (CMH or C-mechano heat nociceptors) in the leg and foot of human volunteers. They found that whereas there was considerable variability between the individual receptors, the majority showed a linear increase in firing rate with increasing temperature of the stimulating thermode. Reported pain ratings from the volunteers also showed a linear increase with both stimulus temperature and firing rate. In skin rendered hyperalgesic by a mild heat injury, increases in reported pain were accompanied by a wide variety of responses in individual receptors, including spontaneous activity, decreased threshold, increased responsiveness to increments in stimulus intensity, etc., most of these being in the direction of increased afferent discharge. They postulated that this diversity was due to the local release of chemical mediators from damaged tissue and to receptor deterioration. They also found that the mean increase in receptor discharge was no longer linerarly related to stimulus

intensity or perceived pain, and indeed, the perceived pain outlasted the receptor discharge by up to 10 seconds. These latter results imply a degree of central processing of pain messages after they reach the dorsal horn.

Other studies have been directed at dissecting out the contributions of different receptor or fibre types, which often get stimulated simultaneously in nature, to perceived pain.

All of the above studies are dealing with peripheral signals. They provide no information on the central processing of sensory data other than frequently supporting the contention that it must occur. Animal experiments have been valuable in elucidating the physiology behind these events, but they are of limited value in the study of perception and in evaluating the experience of pain.

One technique which has shown promise in this regard is the recording of cortical evoked potentials (EP).[3] These are electrical signals which occur over the cerebral cortex following peripheral stimulation. They have 3 main components. (Fig. 4)

1. Farfield EP - 0-20 msec. after stimulus delivery to the periphery. This signal reflects brain stem activity as the sensory impulse ascends. The term "farfield" refers to its distance from the recording electrode.
2. Early nearfield EP - 20-80 msec. after stimulation. This reflects the arrival of the signal at the sensory cortex and is largest over the appropriate part of the cortex.
3. Late nearfield EP - 80-500 msec. This is derived from activity in the association cortex involving recognition, appreciation and interpretation. A specific component of this appears to be related to pain.

Figure 4 displays a typical cortical EP with all the above components. Most of the wave form is very variable and depends on the nature of the stimulus, the site on the body, etc. However, for stimuli causing pain, the peaks designated N163 and P225 appear to be quite stable and vary little across different stimulus types, body locations and different laboratories.

The relevance of these signals to pain phenomena was first put forward by Chatrian and co-workers in 1975.[4] They noticed a characteristic wave pattern on stimulation of dental pulp with an electric current, a procedure that give rise to no sensory activity other than pain. The fact that this wave formation did not occur on stimulation of devitalized tooth convinced them that this was not merely a stimulation or recording artefact.

Subsequent studies[3,7,17,24,25] using stimulation of tooth pulp, lips, fingers, toes and forearm skin where able to reliably reproduce this late nearfield EP under a variety of conditions. The amplitude of this EP was shown to increase with increasing stimulus strength to a maximum which appeared to depend on sensory modality and other undetermined factors. It appeared to be more closely related to verbally reported pain than to stimulus strength in situations where there were discrepancies between the two.[25] Lavine et al.,[17] using a music analgesia paradigm involving taped music and suggestions that this would reduce the discomfort of the painful stimulus, were able to demonstrate a reduced rate of increase of EP with increasing stimulus strength and lower mean EP's and pain ratings for a given stimulus intensity.

Bushbaum[2] divided subjects into "reducers" and "augmenters" on the basis of their EP's. Augmenters show a greater rate of increase of EP with increasing stimulus, are pain intolerant and are unaffected by naloxone. Reducers show a lesser degree of increase of EP with stimulus and are tolerant of pain. Their EP's are enhanced by naloxone. He hypothesized that reducers have a high endogenous opiate function and that opiate analgesia converts augmenters to reducers by boosting this function.

Gehrig and Chapman[7] studied the effects of several pain reducing procedures on EP's and found that 2% lidocaine abolishes the nearfield EP, fentanyl reduces it as do TENS and acupuncture, and naloxone partly reverses these effects.

Harkins et al[11] point out that the wave form identified as the late nearfield EP must be related to A-delta fibre activity as C-fibre signals would reach the nervous system somewhat

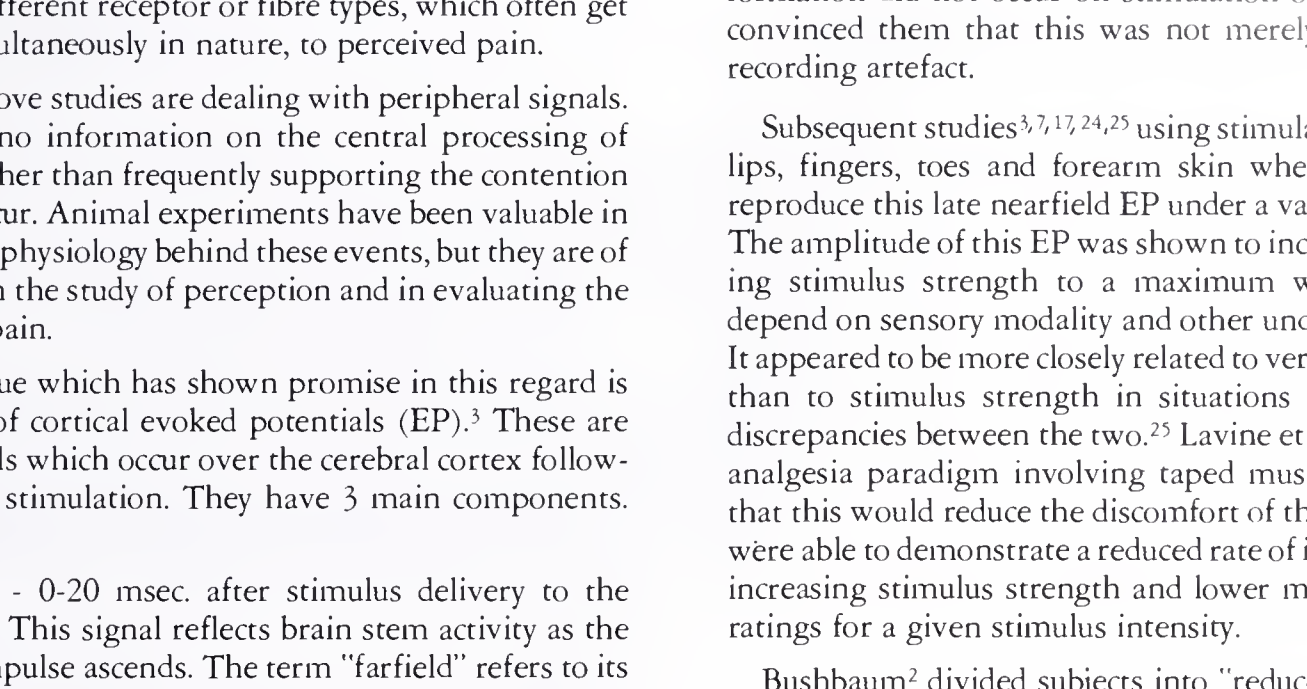

Fig 4 Cortical Evoked Potentials. While farfield and early nearfield signals are variable, the late nearfield peaks designated N163 and P255 appear to be consistently related to painful stimuli.

later. They were unable to detect any consistent patterns which might be related to C-fibre activity. This group also noted that with repeated stimulation the EP's adapted more rapidly than perceived pain. Both these observations suggest that there are likely other modes of central processing of pain information which we haven't detected or investigated yet.

Pain remains a mysterious but virtually ubiquitous human experience. The purpose of pursuing such an intricate understanding of it is undoubtedly to control it - to find its weak spots, to protect our fellow human beings, and maybe some day ourselves, from its devastating onslaughts. Hopefully, this article will have communicated a bit of an appreciation of the nature of pain on a biochemical and physiological level and some idea of the difficulties involved in bridging the gap between physiological data and the understanding of human perception. It deals only in passing with the treatment of pain, the second (or perhaps the first) big issue in pain research, but that is not to deny the importance of work in this area. Hopefully, some day many more of the secrets of pain will be known and many more people will be able to live comfortably with the medical problems they have had to face.

Acknowledgements

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(Cont. on page 52. . .)

A Microcomputer Application in the Plastic Surgery Clinic: Preliminary Report

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Howard Platnick 8T7
Bart Harvey 8T1

In an attempt to better assist the clinical research investigator with data analysis and exploration, an interactive microcomputer system is being developed. Only minimal computer training is required to allow its operator quick entry and access of stored data. Statistical functions can then be performed on cross-referenced data, enabling examination with respect to patient, variable and time. Assessment of this project has provided preliminary insights regarding the role and potential utility of microcomputers in clinical research.

Introduction

Today is unquestionably the age of computers. Their applications have been far-reaching-penetrating the worlds of business, industrial development and modern science. Within the discipline of medicine several valuable applications, including clinical laboratory automation, EKG analysis and physiological monitoring, have been realized. However, in the field of clinical research, widespread computer use does not yet exist. Grant aptly summed this situation by stating,

> "Critical applications (computer technology) in the area of medical and health care, although frequently supposed and increasingly attempted have been disappointing on their impact on the health care system." (as cited in Friedman and Gustafson, 1977).

In an attempt to investigate usefulness of computers as a clinical tool within the Plastic Surgery Clinic, development of a computerized system was initiated. This project began in April, 1984 and when completed its utility to the clinician and clinical research will be assessed. It is hoped that this project will stimulate other similar research studies to help fully realize the capabilities of computing within clinical research.

Objectives

This project was initially motivated by the all too well recognized difficulties encountered while conducting a clinical review of patient records manually. It was believed that the development of a computer system could facilitate this task by providing a more efficient and accurate means of analyzing clinical research data than is currently available.

In order to be successful, the ultimate system had to posess a number of features. It needed the versatility to accomodate several different clinical research projects at any given time. In addition, the system had to be understandable, flexible, and to operate requiring only minimal maintenance. Furthermore, it was felt that the system's cost should be affordale for a single practitioner.

In regard to these, the microcomputers available on the market today appeared to satisfy these requirements. They offer reliability as well as extensive support facilities at a reasonable cost. The needed computer system, consisting of a processor with extended memory capabilities, a display terminal and a printer would integrate easily into any office or laboratory space ensuring easy access and minimal disruption of existing facilities.

The most important design objective was to ensure the system's ease of operation, enabling medical and paramedical personnel, possessing minimal or no computer experience, to successfully run the system. The design of each computerized task was planned to be as "friendly" as possible leading the user through any given procedure by a series of simple, understandable prompts and menu selections.

After defining the project's objectives, the medical literature was reviewed in order to identify and examine any similar systems. Unfortunately, many of the systems encountered employed hardware and financial investments far exceeding our objectives and had been designed for much larger user groups. For example, the CLINFO system had been developed at a cost of several hundred thousand dollars and was intended for use by hundreds of clinical and basic science researchers (Groner, Hopwood, Palley, Sibley, Baker, Christopher and Thompson, 1978). One system, however, was discovered that did possess capabilities similar to our project's needs. This system was an oncology data base, developed by Dr. I. Koven at the Mount Sinai Hospital in Toronto (Koven, 1984). Therefore, in the course of selecting the hardware and software for our project, the adoption and conversion of Dr. Koven's system was carefully considered.

Development

The development stage began with an analysis and review of the data that had been collected since 1977 regarding patients having undergone mammary reductions. As a result of this review and several discussions with the Plastic Surgeon initiating the project, a three-part questionnaire, enabling the encoding of information regarding patients' past medical histories, pre-operative examination, operative procedure, and post-operative follow-ups, was designed and developed. While the restrospective review of previously managed patients was completed, programs for patient data entry, analysis and manipulation were implemented on an upgraded version of the IBM Personal Computer. This microcomputer was chosen over other existing models because of its reliability, extensive software support available, and sizable user popularity. The hardware consists of an internal memory containing a 40 K ROM and a 250 K RAM with an external floppy disk (Williams, 1982). For extended memory, a 10 MB hard disk was included to facilitate storage of an estimated 1,500 patients.

After reviewing the available database software packages, the 'Knowledgeman Data Base" was selected. Other pre-programmed software packages were considered but these were relatively expensive and often inflexible to the need of the clinician. "Knowledgeman" possesses extensive and powerful data handling capabilities, important screen input-output design functions and facilities for the mathematical computations and statistical analyses necessary. Other important features include its flexibility, enabling it to interact with different computer languages, such as Fortran and Cobol, permitting the use of more advanced mathematical functions and file maintenance routines.

Through the use of this software package, a convenient means for storing patient information was developed. As an example, Figure 1 depicts one of the input screens being utilized. The data storage structure that was developed consists of files containing patient's data. From these, information regarding any patient or subset of patients can be easily retrieved for the purpose of review or modification. Figure 2 contains the screen displaying these options to the user. Upon entering a patient's name, the computer quickly accesses the file and displays the requested patient data to the terminal's screen. As well, the system is capable of printing any required reports. To facilitate complete patient records, a recall system was created to provide notification of those patients having missed specified follow-up visits and required clinical reviews.

In addition, programs to enable the clinician-user to explore and statistically analyze patient data were included. With this feature, the medical database can be searched within several parameters, enabling a subset of patients sharing common characteristics, to be identified for display or further analysis.

Currently all of these functions are undergoing rigorous testing. To reach this stage has required approximately 200 person-hours of preliminary system analysis and 550 person-hours programming. At present, test data is being used to verify the system's operation, gauranteeing its accuracy and insuring against any future accidental loss or destruction of information.

Once this process is completed, valuable patient information, encoded on the questionnarie, will be entered into the computer. When this stage is reached, the clinician may began to review and analyze the data, and an assessment of the system's capabilities may be initiated.

In the future, it is hoped that this system will be extended to accommodate other areas of clinical research such as rheumatoid arthritis and breast pain within the realm of Plastic Surgery and benign and malignent colonic neoplasms from the field/discipline of General Surgery. Accomplishing this will require a reconstruction of the patient file for new data and the re-programming of all input and output screens.

```
Record Number: 5

  OFFICE NUMBER :  85-0032


  1. SURNAME      :  Brown
  2. MAIDEN NAME :  Kimberly
  3. FIRST  NAME :  Janet

  4. DATE OF BIRTH  :52/10/18
      (yy/mm/dd)

  5. STREET ADDRESS :  4509 York Mills st
  6. CITY           :  North York
  7. PROVINCE       :  Ont
  8. POSTAL CODE    :  M3A-2F
  9. PHONE NUMBER   :  497-3452

 10. ATTENDING PHYSICIAN :  Dr. Freiberg
 11. REFERRING PHYSICIAN :  Dr. Jones
 12. FAMILY    PHYSICIAN :  Dr. Hartstone
 13. OHIP NUMBER     :  7e5e-7485
 14. SIN  NUMBER     :  447-38e-e25
 15. ADMISSION DATE :  85/ 1/11
       (yy/mm/dd)
```

Fig 1 An example of a data input screen, created using "Knowledgemam".

```
                PATIENT  INFORMATION

  Please select one of the following options
  concerning patient information:  _

      [1]  ADD RECORD

      [2]  UPDATE/DISPLAY RECORD

      [3]  DELETE RECORD

      [4]  PRINT PATIENT INFORMATION

      [5]  HELP

      [6]  MAIN MENU
```

Fig 2 The screen displaying the "Patient Information Options" menu to the user.

Discussion

A preliminary assessment of the system provides the following observations. The development of a computer-assistant for use in the field of clinical research has thus far been

promising. As well as providing accuracy, speed, and reliability, microcomputers possess a vast memory capacity enabling improved access to and storage of patients' medical records. In the past, the manual organization and analysis of clinical research data has been difficult and time-consuming. As a result, it is possible that useful relationships and valuable clinical findings were not discovered. With its vast investigative and search capabilities the microcomputer ensures that a thorough analysis of data can be completed, thus facilitating the elucidation of more useful clinical trends.

However, in the course of designing and developing the system, a few disappointing aspects have also been recognized. The most important of these is the realization that the operation and maintenance of the system, even employing a preprogrammed data base such as "Knowledgeman", will still require active involvement of personnel with adequate computational and technical training.

While many of the computer applications in clinical reserach to data appear intuitively to be of great value, it is difficult to provide any substantial evidence to suggest improvements in patient care. It is hoped that the utilization and evaluation of this system will provide insights regarding the utility of microcomputers in clinical research.

Summary

During the past year a computer system intended to assist with clinical research in Plastic Surgery has been designed and developed. It has been implemented upon an IBM PC microcomputer utilizing the "Knowledgeman Data Base" system, enabling the storage and analysis of information regarding patients having undergone mammary reduction.

With further development, this assistant should become available to its intended researcher-surgeon-user. With this accomplished, as evaluation of the system's utility within clinical research will be undertaken. It is hoped that this development will result in the enhancement of clinical research and patient care.

Acknowledgements

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Koven IH: Principles of An Oncology Data Base For Small Computer. *Canadian Journal of Surgery* 27: 33-34, 1984.

In 20 years there could be no new drugs to imitate

A realistic "full disclosure" of the effects of generic prescribing should include — as a major potential side effect — the reduction, if not outright elimination of new drug research in America.

The root of the problem is simple economics...

At current estimates, it takes approximately $60,000,000 and nine years of hard work to bring a single new drug entity to the point where it can be prescribed in clinical practice. Less than one investigational drug in sixty actually reaches the pharmacy, and many that do have limited application and limited acceptance. Yet each must generate a minimum of $7,500,000 in pure profit each year until its patent expires simply to pay for its development costs.

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Fever

Paul Petrasek 8T7

Fever is the state of sustained regulation of body temperature about an elevated thermoregulatory "set point". It arises through a complicated set of reactions in which pyrogens stimulate reticuloendothelial cells and monocytes to elaborate soluble mediators capable of affecting hypothalamic function. Prostaglandins are believed to play a major role, acting within the CNS to induce fever. Fever may be life-threatening if it progresses beyond 41° C, but likely has beneficial effects if kept within limits. There are many disease states characterized by fever. This paper reviews the current state of knowledge of the physiology of fever and presents some original research on the role of prostaglandins in its pathogenesis.

For thousands of years, physicians have recognized that fever is a common and reliable indicator of disease. The ancient Roman scholar Celsus will surely be known to medical students until eternity for his observation on the cardinal signs of inflammation, 'rubor, calor, dolor, tumor', of which calor, or fever, is an integral sign. Hippocrates is known to have written extensively on fever and the ancient Akkadians of the sixth century B.C. are known to have included in their alphabet, a unique symbol to denote the fever and inflammation which often accompany infection.[1]

It was not until the 19th century, however, when more sophisticated measuring devices became available, that fever was investigated in earnest. In 1875, Von Liebermeister, a German physician, defined fever as a sustained elevation of the body's "set-point" of temperature, a definition which is still useful today.[11] In 1888, William Welch, a pathologist at Johns Hopkins, theorized that body temperature was controlled by the brain, from a subcortical site and that substances elaborated by leukocytes (in response to bacterial pyrogens) were responsible for the upshift of the temperature set-point during fever.[12] Welch's postulate proved to be well ahead of his time; his scheme is still thought to be true and remains an area of active investigation in modern medical laboratories.

Modern Research

Today, research into fever is centred at elucidating its mechanism and hence at developing fast and efficient ways of managing febrile patients in the acute care setting.

i) Phylogeny of Fever

Starting at the very basics, researchers now recognize that fever is an ubiquitous response of *both* warm and cold blooded animals to many different pyrogenic stimuli.[6]

In warm-blooded animals (birds and mammals), fever is maintained by an autonomically controlled increase in heat conservation via increased Basal Metabolic Rate and shivering [illegible] in heat loss via peripheral vasoconstriction.

In cold-blooded animals (amphibians, fish and reptiles), fever is maintained by *behaviourally* controlled mechanisms. In lizards, for example, if one injects pathogenic strains of bacteria, the animals will actively seek out a source of heat, behaviourally inducing their febrile state.[6] The same is true of infected goldfish, who, when febrile, will select shallower waters where they may obtain greater exposure to the sun's warming rays.[8] In both these animals, antipyretic drugs effective in humans (such as acetaminophen) will withdraw the febrile response.[8] (Table 1)

Table 1 The Febrile Responses of Various Vertebrates[8]

	Fish	Reptiles	Birds	Mammals
Live bacteria induce fever	+	+	+	+
Drugs induce antipyresis	+	+	+	+
Endogenous pyrogen produced	?	+	?	+

ii) Purpose

Experiments on many different species of animals exposed to infective agents have proven that the development of fever increases the survival rate. In rabbits infected with *Pasteurella multocida*, for example, there was a 100% mortality rate in a group that received salycilate antipyretics, while only 29% died in another group whose fevers went untreated.[10] Similarly, in lizards infected with *Aeromonas hydrophila*, almost all animals kept at 40°C or 42°C survived, whereas most kept between 35°C and 40°C died.[7]

Several beneficial host responses to infection have been proven to be enhanced at higher than normal body temperatures.[6] Among these are:

- increased leukocyte mobility
- increased lymphocyte transformation
- increased bactericidal activity of leukocytes
- enhanced interferon effect
- decreased lysosome stability

Additionally, elevated body temperatures have been correlated to decreased levels of plasma iron, a metal necessary for the growth of many bacterial pathogens.[2]

In humans, it is unusual to observe a fever progress to over 41°C. Death due to hyperthermia (hypothalamic shutdown of autonomic functions) is almost always the result beyond this temperature.[5]

iii) Mechanism of Fever

For a long time, it has been recognized that body temperature is controlled by neurons of the anterior and preoptic nuclei of the hypothalamus. Fever arises as a result of a complicated series of cellular events which appear to raise the temperature set-point of this area, inducing thermogenesis.

In the vast majority of fevers, the process of raising the set-point is initiated in the bloodstream, through the introduction of a pyrogenic stimulus. There are literally hundreds, perhaps thousands, of stimuli which are "exogenous" pyrogens — anything from gram-negative bacterial endotoxins to the antigen-antibody complexes encountered in autoimmune diseases.[1] Such a diversified distribution is probably the reason that fever is a common symptom of many different disease processes, in addition to infection. (Table 2)

The common denominator behind all "exogenous" pyrogens is that they are universally capable of acting upon reticuloendothelial cells and monocytes to induce the formation of an "endogenous" pyrogen, a protein of MW 13-15 KDa.[2]

During fever, the "endogenous" pyrogen disseminates through the blood, targeting the anterior hypothalamus, where it probably does not cross the blood-brain barrier. Rather, at the capillary endothelial cells of the blood-brain barrier. Rather, at the capillary endothelial cells of the blood-brain barrier, a "secondary messenger" is produced which acts directly (or possibly through a tertiary messenger) to raise the set-point of thermoregulatory neurons and induce fever.[4] In warm blooded animals, fever is established by largely unknown mechanisms (possibly neural or hormonal) which increase the Basal Metabolic Rate, cause cutaneous vasoconstriction and shivering. (Figure 1)

Today, there is striking evidence that the "secondary messenger" produced at the blood-brain barrier is a prostaglandin, specifically, PGE_2.[3]

Prostaglandins are a group of naturally occurring C_{20} carboxylic acid derivatives believed to be produced ubiquitously in the body. They are derived from cell membrane phospholipids and their cleavage product, arachidonic acid. (Figure 2) Prostaglandins exert many important effects throughout the body. PGI_2 is an important inhibitor of platelet aggregation, for example, while PGE_2 and $PGF_{2\alpha}$ are endogenous stimulators of uterine smooth muscle contractility.[13] Non-steroidal anti-inflammatory analgesics are potent inhibitors of prostaglandin synthesis and, not coincidentally, are among the most effective antipyretics in use today.

Table 2 The Association of Fever With Different Disease States[1]

Disease Catergory	Fever Usually Prominent	Fever Often Present
Acute Infection	any septicemia	Gm. pos. bacteria (exotoxin formers) i.e. Diptheria Tetanus
Chronic Infection	malaria	many bacterial infections i.e. osteomyelitis
Tumors	Acute leukemias Hodgkin's disease	Histiocytic Lymphoma Ewing's sarcoma
Collagen vascular diseases	Lupus Juvenile R.A. Acute rheumatic fever	Polyarteritis nodosa Giant cell arteritis
Hypersensitivity	Serum sickness	Sarcoid
Acute inflammation without infection or allergy	Pulmonary embolus Crush injuries Acute gout	M.I. etOH hepattis Inflamm. bowel disease
Abscess	Any with access to the circulation	Smaller or draining
Other		Dehydration (children) Delirium tremens Atropine poisoning CNS bleed

Fig 1 Steps in the Pathogenisis of Fever

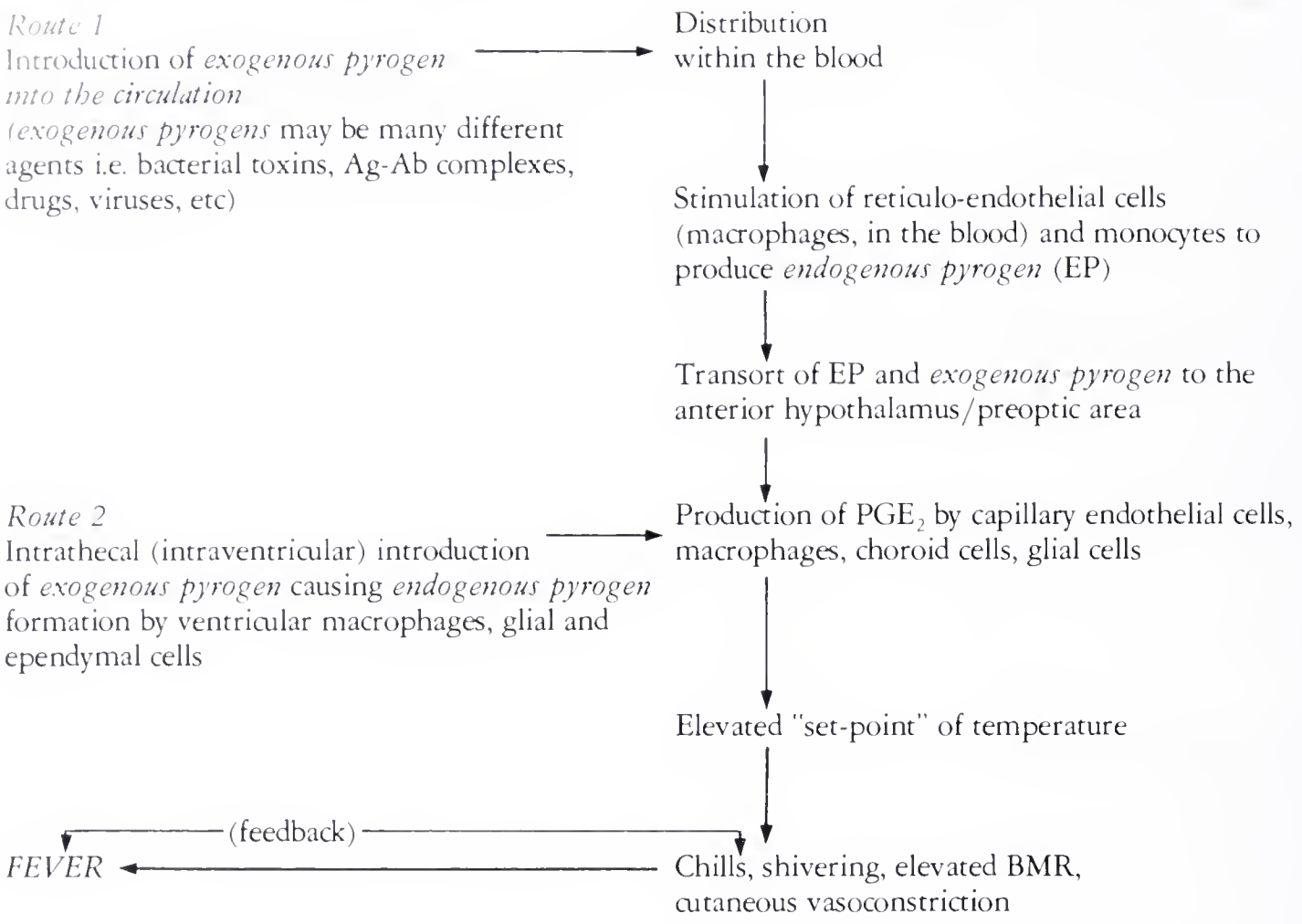
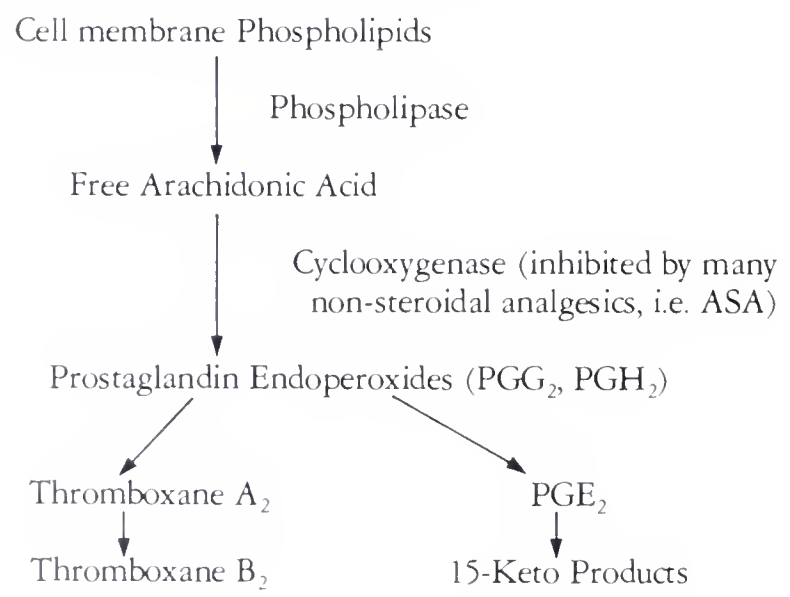

Route 1
Introduction of *exogenous pyrogen into the circulation*
(*exogenous pyrogens* may be many different agents i.e. bacterial toxins, Ag-Ab complexes, drugs, viruses, etc)
Distribution within the blood
Stimulation of reticulo-endothelial cells (macrophages, in the blood) and monocytes to produce *endogenous pyrogen* (EP)
Transort of EP and *exogenous pyrogen* to the anterior hypothalamus/preoptic area
Route 2
Intrathecal (intraventricular) introduction of *exogenous pyrogen* causing *endogenous pyrogen* formation by ventricular macrophages, glial and ependymal cells
Production of PGE_2 by capillary endothelial cells, macrophages, choroid cells, glial cells
Elevated "set-point" of temperature
(feedback)
FEVER
Chills, shivering, elevated BMR, cutaneous vasoconstriction

Fig 2 The Prostaglandin Synthesis Pathway[13]



iv) The Role of PGE_2

Research in our laboratory has strongly implicated PGE_2 as being part of the pathway leading to the development of fever. Using cats, we have developed an experimental method for inducing fever and then sampling CSF (from the area around the thermoregulatory centre), which we later analyse for PGE_2. Specifically, we surgically implant cannulae into the third ventricle of cats' brains, locating them next to the temperature-sensitive hypothalamic area. Subsequently, in a typical experiment, we "infect" the cats with liquid *E. coli* endotoxin (a common exogenous pyrogen) by either intravenous or intrathecal injection (ie. injection through the cannula directly into the CSF). We monitor PGE_2 levels in the CSF throughout the subsequent fevers and record and animals' skin and body core temperatures.

Figure 3 shows the typical temperature profile of a cat whose CSF was injected with *E. coli* endotoxin. Immediately after injection there is a "latent" period delay, during which time the endotoxin sets the endogenous pyrogen/prostaglandin synthesis pathway of Figure 1 in motion, to develop a fever. As the animal's core temperature rises, during the "uprise" phase, its skin temperature decreases, indicating cutaneous vasoconstriction and heat conservation. Eventually, the fever "plateaus" at the new set-point of body temperature. Such a temperature profile would be similar to that of any febrile human, under similar circumstances.

As Figure 4 indicates, in a series of seven experiments, we consistently noted that PGE_2 levels in the CSF of the cat increased, in concert with increasing body temperature, during fever development. Such a finding could indicate one of two possibilities:

i) That PGE_2 plays a role in the initiation of fever, in relation to its concentration in the CSF.

ii) That PGE_2 is an inactive byproduct of the fever process, which increases in concentration relative to rising body temperature.

We believe that (i) is correct and are able to support such an hypothesis with the fact that we found PGE_2 levels to be elevated in the "latent" period of fever, after endotoxin injection but before the onset of temperature increase. Our hypothesis is further supported by the research of others, who have found that intrathecal injections of PGE_1 or PGE_2 may

directly initiate fevers.[9]

One question which we are not able to answer from our research is whether PGE_2 is the final step in the pathway of fever development. It is possible that there are pyrogens different from PGE_2 that are formed subsequent or concurrent to PGE_2 prodution. Earlier studies have implicated thromboxane A_2, another prostaglandin, as being elevated along with PGE_2 during the "uprise" phase of fever.[5] Time and further study may one day confirm such an alternate mechanism.

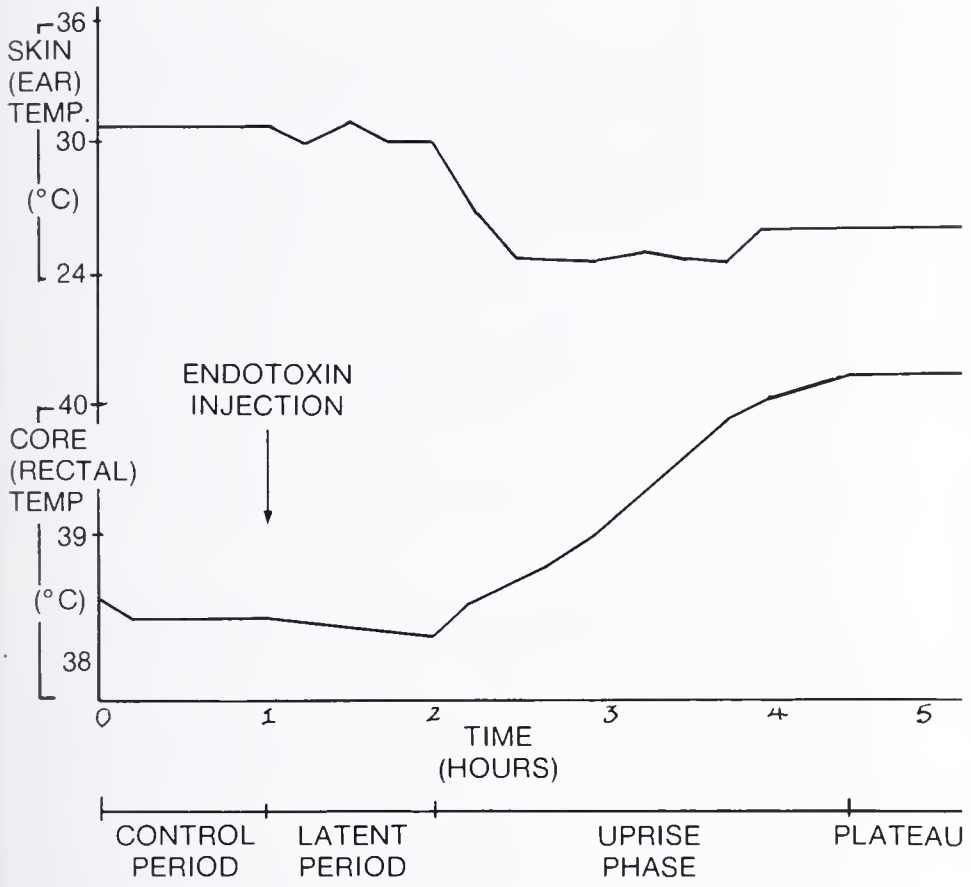


Fig 3 A typical fever profile after the injection of *E. Coli* endotoxin into the CSF of the third ventricle of the cat brain.

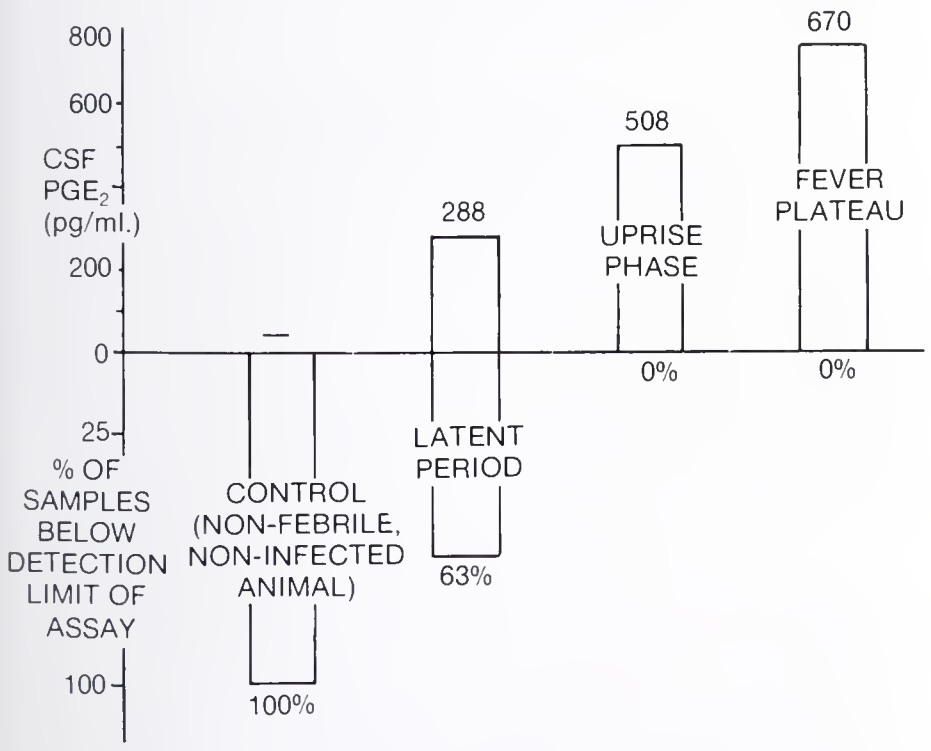


Fig 4 PGE_2 levels in the CSF of the cat during different stages of *E. Coli* endotoxin induced fevers. (values are averaged from seven different experiments involving five cats, PEG_2 measured by radioimmunoassay)

Conclusion

Detailed investigations into the exact mechanism of fever seem painfully far detached from the emergency department setting where one is presented with an acutely febrile patient accompanied by despondent immediate family. This paper offers no magic cure for such a situation, but rather, is intended to enlighten one to the facts that fever is a widespread response across the animal kingdom to many different stimuli, that it may have a beneficial effect on survival (if kept within limits) and that it arises from a complicated set of reactions involving macrophages, monocytes, capillary endothelial cells and hypothalamic neurons.

Prostaglandins appear to play a major role, within the CNS in causing fever. The prostaglandin link is especially interesting, since non-steroidal analgesics, such as aspirin, are inhibitors of prostaglandin synthesis. If the old adage that "good science makes good medicine" is true, then there is no doubt that attaining a greater understanding of the role of these agents in fever will hasten the development of new and more effective antipyretics.

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(Cont. on page 49. . .)

A Modern Cinderella

Katherine McCuaig 8T5

Janice Harrington had never seen as many fat women in small swimming suits as she did on the beach at Mombasa.

From their gutteral tones and almost stereotypical blonde, square-angled, Teutonic heaviness, she deduced that most were Germans on package holidays. Spread-eagled on vinyl-covered lounge chairs, arms rigid and fingers splayed to broil every pore possible, they basted like Christmas turkeys in the tropical sun. Rivulets of tanning butter oozed between the rolls of fat, soaking into their garish beach towels, sticking to the vinyl cushions and pooling between their pendulous breasts. At midday, after ravaging the hotel buffet like hoards of hungry schoolboys, they rolled over, virtually en masse to bake the other side. Otherwise they never moved, except to reapply more cream or lotion, or pull down a bikini strap to prevent the horror of tan lines. Immobile, with their eyes shut loosely and their faces carefully expressionless in order to avoid any laughter lines or wrinkles, they concentrated on their sun tan with the singleminded intensity of a zealous missionary plotting the conversion of the pagan masses. Oblivious to the scenery surrounding them—the carefully pruned tropical vegetation, the weathered dhows just offshore, and the muffled sound of the breakers, they focused only long enough to stare malevolently at any presumptuous palm trees which dared to filter out their sun. Janice stared at them with a nauseated, fascinated horror: littering the beach and obscuring the picture postcard view of the aqua green Indian Ocean, they were as unappealing and incongruous as chickenpox on the face of a teenage beauty queen.

They were so tasteless and repulsive. She wondered guiltily if she were becoming hopelessly staid and provincial, only a few years out of university. Was this the same girl who had once hitch-hiked across North America, boycotted grapes for two years, and laboriously embroidered "Do Your Own Thing" on her back pack, condemning a whole nation of tourists so hastily? It was undoubtedly good for her character, she told herself sternly, that she had come to Africa. Even a onetime borderline hippie could get set in her ways.

Neither beautiful nor plain, she was a woman those meeting her for the first time would describe as "still young" rather than "young": slim, but tending to pudginess around her hips, giving promise of a definite pot-belly before she was fifty; indeterminate, chin length, mousy brown hair with threads of barely noticeable gray, parted slightly off-centre and tucked behind her ears; clear skin without much colour and pale [illegible] gray eyes. She considered make-up bothersome, so never [illegible] and her wardrobe generally consisted of an unins[illegible]ction of knee-length skirts and crew neck sweaters [illegible]ned browns, blues and greens. Unfashionable, she [illegible] being dowdy; a soft-spoken rather earnest young [illegible] was usually labelled as "nice" or "pleasant" by those who knew her. Her character didn't seem to warrant strong adjectives.

She worked as an executive assistant in the Waste Management Branch of the Ministry of the Environment, preparing policy papers which, she was cynically aware, few read and no one implemented. On paper (certainly on her resumé) her life seemed appropriately varied and interesting: aerobics classes three times a week, drinks with friends on the weekend, plus or minus a movie, and even the odd fling with a man she met at a bar when she was sure he didn't have herpes. So why, she had demanded of herself, was she so restless and bored? Staring in the mirror one bleak November morning, she had reflected almost bitterly that her life seemed to be as well-ordered, sensible and dull as her appearance. She felt as spontaneous and uninhibited as a Victorian school mistress.

Like a pinball machine with the spring pulled tightly back, she was fully primed when the Developing World Environmental Conference literature landed on her desk, with a beguiling assortment of glossy photos of elephants grazing in front of Mt. Kilimanjaro and luxurious safari lodges. She had snatched the opportunity like an alcoholic reaching for his first drink of the day. With the smooth persuasiveness of a vacuum cleaner door-to-door salesman, she managed to convince the department supervisor to approve the government's paying half her air faire plus conference expenses and tagged two weeks of her vacation time on at the end of the trip.

Nairobi: exotic, seductively foreign, the very antithesis of the damp, gray respectability of Toronto in February. A city of contrasts, piled helter-skelter on top of one another: the red clay that caked your shoes after a rain shower and left a light coating of dust on all your clothes; the Camelot-like climate with its sunny days and cool, dark, mountain nights; the hot, bright equator sun which set so quickly that day and night collided abruptly with one another, with no foreshadowing dusk to cushion the blow; the corn cobs roasting on makeshift grills of wire and rocks in the shadows of cement office towers; the African women in their polyester dresses, khangas knotted casually, incongruously, around their waists; and the omniprescent children, hanging placidly like lumpy packs on their mother's backs. Only hours after her transatlantic flight, almost stuporous with jet lag and sleeplessness, she had stood on the corner of Uhuru Highway and Kenyatta Avenue, gaping bemusedly at the matatus careening into the curb, stealing the passengers away from the lumbering city buses. Impatiently fending off the con men hawking plastic elephant hair bracelets, she felt the same exhilaration she had experienced a decade earlier when she had stared down into the foaming rapids of the Fraser River Canyon. Here, she exulted, anything was possible.

In the days which followed, Nairobi lived up to its promise but not, she decided with a tinge of disappointment, its potential. Perhaps it was the conference—it imposed an atmosphere of hypocritical respectability. The men spent the nights crawling through the shadowy, sleazy bars on River Road, sampling the beer and prostitutes, occasionally getting rolled, and then appearing earnest and hungover at the afternoon sessions. She spent her nights in the Big Five bar or the Norfolk and, although she ordered Tusker or White Cap instead of her regular brew, it wasn't much different from North America. Barflies, it appeared, were the same world over. Her one foray into the local culture, aside from bargaining for sisal bags and soapstone carvings at the city market, was a night spent at the Starlight club, dancing to African music and watching the local hookers efficiently hustle the half dozen or so stylishly casual prep school types drinking at the bar. She spent forty minutes trying to decide if their accent was Australian or South African, before she gave up and returned to her hotel.

But Nairobi was a city, she reasoned, her old "back-to-the-land" bias resurfacing, and cities were rather like Down's Syndrome children: they resembled one another more than anything else.

With renewed optimism and fourteen other aspiring adventurers, she crawled into a refurbished army truck the morning after the last session, and bounced over endless miles of rock stewn dirt roads. Sandwiched between a British schoolteacher and ex-Peace Corps worker just back from Tanzania, she listened ad nauseum to an aging bookstore owner try to seduce a Harvard law student. It was a far cry from the Nairobi businessmen getting soused at the hotel bar. The heat in the truck seemed to dissolve the ever-present dust in their sweaty pores, coating their skin with a slimy crust. She and her fellow travellers peered through the murky windows, snapping photos of zebra or elephants grazing on the grasslands, sneaking shots of the Maasai huts and long-legged warriors striding along the roadside, or peering at termite hills and bleak volcanic rocks on the way to Lake Turkana. The backs of their legs stuck to the warm rubber of the narrow seats, and the stale aroma of body odour and exhaust fumes was all pervasive. Every night they set up camp, aided by a surly, overbearing drive-cum-guide, fending off mosquitos and showering when they could. In twelve days Janice's mousy brown hair lightened slightly to a tan shade (ending her recurrent dilemma over whether or not it would be inexcusably vain to highlight it), her skin bronzed, and she lost fourteen pounds, partly from a mild case of dysentry, and partly from picking at her food. She had begun to question the hygiene of the cooking on the fifth day when she watched the cook scramble eggs in the basin in which the school teacher had just finished soaking his infected foot.

Despite (or perhaps because of) the hardships, she enjoyed the trip—upheld by a feeling of virtue, she had "gotten back to the land", and "paid her dues", as she wrote smugly on the postcards of Samburu warriors and the Rift Valley which she mailed home. Nostalgically, it reminded her of hitching a ride in the back of a pick up truck from Thunder Bay to Saskatoon eight years earlier. She couldn't be getting old, or set in her ways, she assured herself, if she could still rough it. Besides, like a delicate French pastry or exotic liquer at the end of a filling but bland roast beef dinner, the luxurious decadence of Mombasa dangled in the offing. Her liberal conscience had felt rather guilty about booking four days there, with all those starving children in Ethiopia, but she consoled herself that she *had* put in two weeks on a rackety bus trip.

The glamour of Africa had eluded her thus far, but Mombasa, she told herself as she relaxed in the overnight train, sipping wine in the dining car and revelling in the colonial atmosphere, was the stuff of which fantasies are woven. The steamy tropical heat enveloped her slowly as the train neared the coast, and the palm trees and coconuts flashing by the window seemed straight out of a *National Geographic* article on the South Sea islands rather than the African jungle.

Her five-star hotel sprawled on the Indian Ocean, about ten miles north of Mombasa town itself. As a nodding concession to the Arabic flavour of the coast, it was almost middle-Eastern in design, with low-lying, white stucco buildings and carved, arched doorways. Internally it was thoroughly Western; air conditioning, bidets in the washrooms, two bars and even a large swimming pool for those who found the ocean unmanageable or too far from the bar.

What struck her, like a cold, wet beach towel flung viciously in her face, were the Germans. They enraged her. Their very presence shredded her candy floss notions of a sophisticated tropical paradise and mocked her fantasies of a glamorous, Cinderella-like affair. Like mosquitos on a hot summer night, she thought resentfully, they seemed to take over everything, from the bar to the windsurfers. As a sulky, spoiled teenager might, she catalogued all their faults, real and imagined; they grabbed the lawn chairs before anyone else got to the beach in the morning. Their children threw tantrums at the poolside, jumping in, cannonball style, oblivious to those swimming. And they descended upon the nightly buffet dinner like rabid shoppers on a bargain counter at a Boxing Day sale.

But it was the middle-aged, bordering on elderly, gray-haired Teutonic women flaunting their young African gigolos which incited her contempt. It was pathetic and disgusting, she thought righteously, sipping a beer the first night, watching them giggle like school girls while they danced on the poolside patio, their hands caressing the backs of the men, until the couples drifted away into the hot night. Part of her mind was rather appalled at her intense reaction; mulling it over on her third beer, she wondered morosely if she were becoming an old maid, the type of dour harridan who telephoned the principal to complain about the high spirits of the school children. Or maybe it was just culture shock. In Toronto, she had deluded herself that she was fairly sophisticated. Even in Nairobi she had contrived to amuse herself. But under the glare of the poolside lights and the seductive shadows of the palm trees, she felt hopelessly provincial.

Like a fifteen year old girl at her first cocktail party, she earnestly tried to participate — skin-diving off a coral reef the first afternoon, sailing in a catamaran, even trying to arrange ind-surfing lessons — but she felt too shy, too awkward, to break into the cliques of urbane Europenas surrounding her. She had always mocked the sterotypical American tourist; now, she wistfully yearned for a glimpse of a balding, pot-bellied middle-aged man in bermuda shorts and a baseball cap, accompanied by a stout woman in a floral bathing suit

beach coat. As she settled down with her novel on the beach the second afternoon, she convince herself that what she really needed was a relaxing, not exciting, vacation.

Are you the woman who was asking about wind surfing lessons?" She raised her eyes from the page to stare into a slightly pock-marked, high cheek-boned, clean shaven, chocolate brown face. He was thin, and his khaki-coloured cotton pants slipped partly over his hips, giving him a casually seductive appearance. His chest was bare, sprinkled only sparsely with a smattering of black curly hairs. "I guess so," she responded cautiously, returning his stare in the same assessing manner. He seemed innocent enough, but she vaguely distrusted his assured manner. She had been fleeced of forty dollars by two con men pretending to be refugee Ugandan students at the Nairobi Conference centre only three days before, and was reluctant to agree to anything, no matter how innocent it appeared.

"They're available about a mile down the beach." He gestured with a sweep of his arm, indicating a recently opened luxury hotel in the distance. "Do you see the booth?" She squinted, but the glare of the sun off the sand made it impossible to be sure. "Come on," he smiled guilessly, and she felt almost ashamed of her suspicions, "and I'll show you."

His name was Randolph and he did odd jobs around the hotel, he informed her, as they tramped along the sand. A Luo tribesman, he had lived for a few years in Nairobi, working as a waiter at the YMCA; but the coast seemed to offer more opportunities. She felt even more mean-spirited when he walked the length of the beach with her and sorted out the terms of her lessons, without hinting for a tip. He appeared so obliging, she felt it was degrading to offer him twenty or thirty bob for his aid. Moreover, his was the first friendly overture she had had in forty eight hours, and she was pathetically grateful. Maybe she was wrong about Mombasa—maybe it did have potential to give an eager Cinderella a fairytale ball. Even the German children seemed more tolerable after Randolph arranged to take the bus into town with her the following day to see Old Fort Jesus.

He confidently steered her through the narrow streets, guiding her past the fresh-caught stench of the fish market to sneak an illegal picture of the dhows bound for Lamu in the old harbour, and pointing out the better coffee and spice shops. He paid his own way, and occasionally hers when she was short of change; he made no secret of the fact he was chronically short of funds, but there was an air of friendly dignity about him that just missed being aloof. Within twenty four hours she had fallen headlong in love, like a ten year old with a crush on a rock star. Her hands almost shook as she chose her dress—a conservative, halter top affair—for dinner that night. After a moment's indecision, she put on her skimpiest underwear. She could almost hear her mother's voice intoning when, as a pre-schooler, she had shoved her feet into rubber boots, "Better safe than sorry".

Lust was a heady emotion, she decided dreamily, several hours later, particularly if one had difficulty separating it from love. Not that it really mattered—part of the sheer enjoyment of wallowing in it wholeheartedly was its ephemeral nature. Even though she held rigidly democratic notions, she was hardly likely to settle down with an African beach bum.

In true hero-style, he stayed the night, and they ordered in a Champagne breakfast the following day. For the first time since her arrival she felt glamorous, attractive—able to take on any hard-edged, German women, she thought beligerently, on their own terms. What did it matter if she got a puzzled, almost reproving stare from the normally chatty chambermaid? People could be such bigots. Her first affair with a Black man. She revelled in her liberal disregard of narrow-minded public opinion as she sipped her coffee.

For two days they were inseparable. He took his meals with her (discreetly organizing his payment with the hotel staff for she never saw money change hands), supervised her wind-surfing so that by the last lesson she could actually stand up and sail a few feet on a calm day, and, when they weren't strolling along the shore, stretched out possessively next to her on the beach. Her novel was forgotten, pushed carelessly under the dresser their first evening together, and never retrieved. Sometimes she would stare at him surreptitiously, his head cradled by a rolled up beach towel, and try to memorize the moment. She told herself, startled and almost fearful, that she was perfectly happy.

Her plane to Nairobi left at eight p.m. Thursday, so they had a private dinner together at the bar early that evening. She wasn't disappointed—it seemed more appropriately romantic to have a last intimate meal. He held her hand as they wandered back to her room. She wondered nervously if there would be time for anything other than an exchange of addresses—she still had to slip her toiletries and bathing suit into assorted plastic bags and shove them in corners of her hand luggage.

He seemed quiet, almost shy, back in her room, fiddling with her tube of sun tan oil, and trying to make desultory conversation. Her impending departure was obviously preying on his mind, she thought sorrowfully, but with an irrepressible tinge of powerful satisfaction. It was, after all, rather flattering to leave someone devastated.

"What about the money?" he demanded abruptly, looking up suddenly from the tanning lotion top he was methodically twisting off.

"What money?" she responded blankly. She couldn't recall borrowing any.

His tone was a shade defensive, even irritated. "*My* money."

"For what?"

He shrugged, as if to pretend it didn't matter. "For showing you around and...other things," he finished vaguely but firmly. "What else?" His tone was calmer, like a store owner explaining the cost of a choice cut of beef to a perplexed customer.

What else? Her voice reiterated blankly in her mind. Shocked, she felt one side of her personality—the logical, analytical side—begin to control her mouth, while she herself refused to comprehend what was happening.

"Do you mean," she said carefully, like a doctor summarizing a complicated medical history before he committed it to paper, "that you expect me to *pay* for your company the last two days? That we just didn't meet coincidentally on the

beach and click together?" Even as she asked, she realized the question was a lame one. How could she have been so naive? How could anyone—particularly a man with no real livelihood—possibly do nothing but amuse her for two days and expect nothing tangible in return? She felt slightly nauseated. It was so degrading, so sordid, as if she were one of those German women she had condemned so scornfully, flaunting her pseudo-conquest. Perhaps that was the worst of it—the wholesale destruction of her pride.

"How much do I owe you?" She tried to sound nonchalantly businesslike, but succeeded only in appearing tight-lipped. "I wouldn't want to be stingy."

"Whatever you think it was worth." His tone too was stiffer.

"Five hundred shillings? She rummaged in her pocket and pulled out some crumpled bills. "No, that's a little cheap—after all, the sex was good. Would another five hundred cover the sex, do you think?"

"You're angry." It was a statement, not an accusation. He stared resentfully at her face for a moment, then reached out and picked up the bills she had contemptuously thrown in front of him on the bed. He stared at the president's picture for a moment, then stuffed them in his pocket, lashing out in a manner which was even more convincing by virtue of his self control. "You knew I had no money. What did you think I lived on—water from the Indian Ocean? You Americans, so innocent, so self-centered—"

"And stupid."

He continued, ignoring her bitter interjection. "Or perhaps the scraps from those elegant buffets? Look, you told me yourself you were bored silly your first two days here, that your holiday was a failure...you were willing to spend a hundred dollars a day at the game parks *watching* the lions and elephants screw, but you're too cheap to pay for the fun yourself." He paused, but she merely continued to stare woodenly, and his expression hardened. "Is it any less enjoyable," he demanded sarcastically, "because I made a bit of money?"

His question was almost rhetorical, but she answered nonetheless. "I thought the time we spent together was payment enough."

He shrugged, not bothering to respond. She turned to stare out the window and breathed in deeply several times to steady herself. God forbid, she couldn't cry. She *wouldn't* cry—not now, not in front of him. But she couldn't bear to look at him, she was so mortified, so embarrassed. Oh God, how could she have been so naive..."Did the hotel staff know?" she asked dully, after a moment.

"Of course."

Well, that explained the disapproving stares, she thought, with analytical detachment. They weren't bigots, just moralists. It was an oddly comforting thought; that the chambermaid at least had believed her to be above this...

He stood awkwardly at the foot of the bed for a half a minute, then shrugged again, as if to finish the conversation. "Your plane leaves in just over an hour—we'd better get your bags in a taxi." He looked at the motley collection of suitcases and tote bags. "Do you need help?"

It seemed like such a non sequiter, such an insensitively prosaic question, that her gut knotted up in revulsion. There was a bilious taste in her mouth. No, she wanted to scream, not from you. But the remnants of her pride dictated that she try and appear blasé and indifferent. Thank God she was leaving Africa. "I might as well get my money's worth," she responded nastily. "Take the big case, please."

Like a mother ignoring a two year old indulging in a temper tantrum, he picked up the bag and marched out the door. She followed a quick pace, about ten feet behind until she passed the gift shop. Surveying it thoughtfully, she paused at the rack of postcards outside.

"Tell the cab I'll be there in a minute," she called out suddenly, then impulsively turned to go in, an odd notion forming in her mind. She grabbed a dozen of the most glamorous scenes she could find—moonlit beach nights, dawn over the Indian Ocean, the night life of Nairobi. She would write postcards on the plane, she decided with renewed vigor. The knot in her stomach eased slightly, and her nerves seemed to steady. She would make sophisticated allusions to passionate Africans and love at first sight. As her literal-minded grandfather had been inordinately fond of saying, no one knows you have a boil on your behind unless you tell them. Surely that applied to emotional sores as well?

He had left by the time she reached the waiting taxi, but her bags were piled neatly in the trunk. Besides, she continued to muse more buoyantly as she slid into the back seat, no one has ever known what really happened when Cinderella or Sleeping Beauty first met the handsome prince. We only know the story they chose to tell posterity. And everyone knows the best fairytales have happy endings. Perhaps, it wasn't whether you won or lost, or even you you played the game, but how you interpreted the results.

Industriously, she began to scribble a postcard.

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1st Prize:

Sonnet to a Friend

Go breathe the wind that blows across the West,
Discover the mountains that peak above the sky
And touch the sea, the streams that split the forest
And songs that fly to trees are Nature's cry.
You left to follow the calling of the soul,
Escaped the pillowed prison laced with love.
I think of my success, but what a toll!
To feel not life nor see the stars above.
Go seek the passion of winds symphonic,
With strength of mountains spurn the Hollow Men,
Let streams and rivers cleanse with strains poetic,
Confine the Brain, and feel with Heart. And when
In time your journey leads you by this way,
Please tell me, "Did I pay too much to stay?"

Ambrose Cheng, 8T8

2nd Prize:

Subtext

Words
I'd hardly dare imagine
Fill my thoughts
Silent subtext
To the images
Of you

Pretty, moving
Pictures
Shapes
Twist and turn
Grasping my
Attention

Weak in the knees
Victorian in
My quiet
Passion
I confine my
Thoughts
To ill-shaped
Rhyme

Words — taking on
A life their own
Spring unguarding
From my frozen lips
[illegible]ching
[illegible]

Be still
Break o[illegible]

Lindsay Davidson 8T6

3rd Prize:

Flowers

They always stay too long —
flowers, gaping tumid
in their final flourish.
Overripe matrons,
spreading in billowy bright frocks.

And how ruthless to push those organs in
among the coffee and bits of egg:
We wince at the obcenity.

So they remain,
lilting limpid
until the crisp sets in.
But it's too late:
They should be gone.

Sentimentality is overwhelmed
by the curl and crackle.

The line's too fine
between
symbol
and intent

Kinsley Watts 8T7

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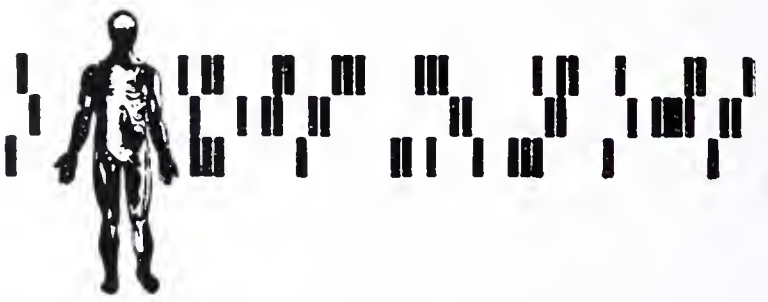

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Multiple Bilateral Pulmonary Nodules

Anne Marie Shorter, M.D.,
Robert H. Hyland, M.D., F.C.C.P.,
Robin R. Gray, M.D.

Diagnosis: Pulmonary Sarcoidosis

A thoracotomy was performed and a wedge resection containing two well-demarcated nodules, was taken from the right middle lobe (Fig. 3). The nodules were made up of granulomata with some central caseous necrosis surrounded by epitheloid cells, a few giant cells and chronc inflammatory infiltrate composed of lymphocytes and plasma cells. There was no evidence of vasculitis. Specific staining and cultures were negative for fluorescent mycobacteria and fungi. A diagnosis of sarcoidosis was therefore made. The patient's post operative course was unremarkable. Pulmonary function tests one year later were unchanged. Follow-up chest roentgenograms eighteen months after the operation showed no changes, and the patient continued to feel well on no therapy.

Sarcoidosis is a chronic generalized granulomatous disease of unknown etiology. It is characterized by noncaseating granulomas that can be found in almost any organ, most commonly the lung. The disease is more frequent in temperate than in tropical climates. There is no clear sexual predominance and it commonly occurs between the ages of 20 and 40. People of the Chinese origin, even those living outside of China, are resistant to the disease. Sarcoidosis is rarely in South American or African blacks, whereas blacks in North America have an increased susceptability.

Radiologically, sarcoidosis commonly presents in one of three classic form: as bilateral hilar lymphadenopathy, as diffuse pulmonary disease with hilar enlargement, or a diffuse pulmonary infiltrates alone. The majority of cases (up to 88 percent) have lymph node enlargement with or without parenchymal involvement. Large nodules are uncommon in any of the presentations.[1] Several authors have indicated that large coin-like lesions usually associated with metastatic malignancy may rarely occur in sarcoidosis. Felson, for example, describes five cases of sarcoid presenting with as multinodular pattern.[2] All these patients were black and in all five the course of the disease after diagnosis was stationary or even regressive. Littner et al found three patients with large pulmonary nodules in a series of eighty-nine sarcoid patients whose disease had been confirmed by biopsy. (Only one of the three was black)[3].

A syndrome called Necrotizing Sarcoid Granulomatosis has been described in which patients roentgenographically have pulmonary nodules often in association with bilateral hilar lymphadenopathy. The distinctive pathological feature in these patients is the presence of a granulomatous vasculitis which was not seen in our patient. These patients have a good prognosis and it has been speculated that this syndrome may be a variant of conventional sarcoidosis rather than a more sinister vasculitis.[4]

The patient, therefore, is a reminder of this unusual presentation of sarcoidosis which appears to have a very good prognosis without any specific treatment.

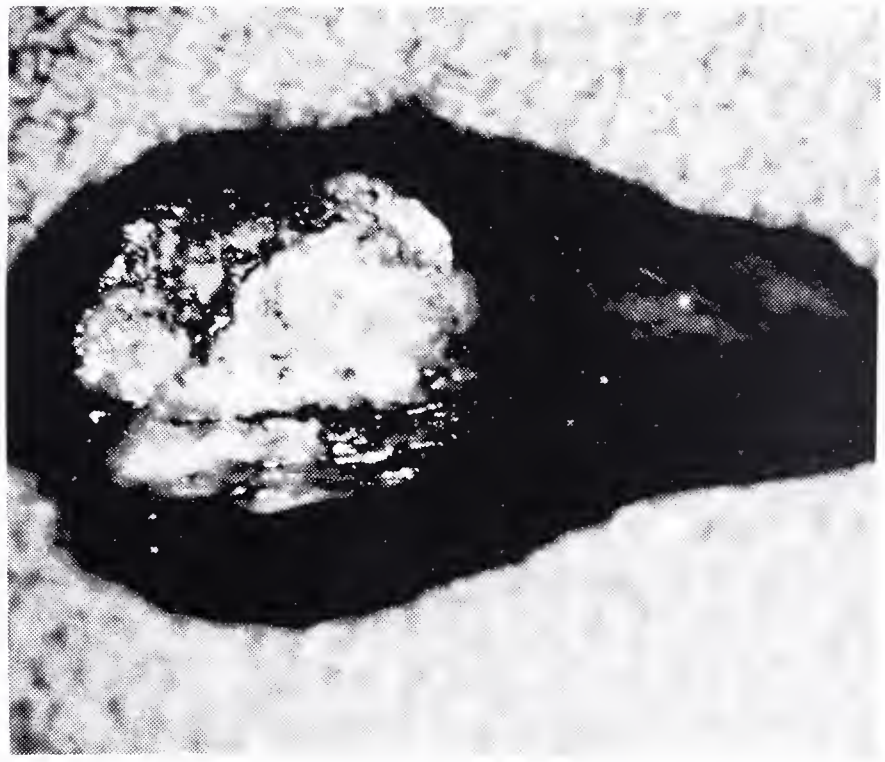

Fig 3 Pathological specimen, taken from right middle lobe, which contains two well circumscribed nodules.

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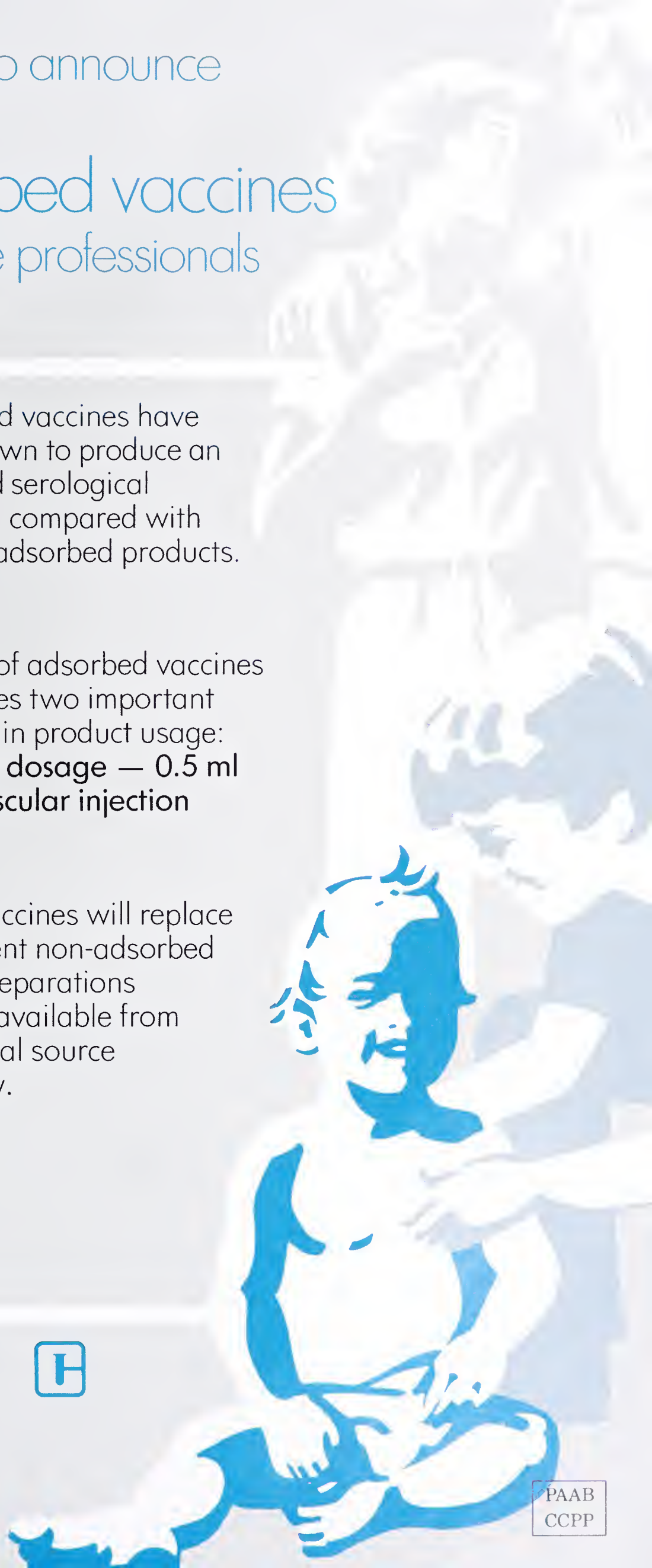
Diphtheria and Tetanus Toxoids and Pertussis and Poliomyelitis Vaccines Adsorbed
Active Immunizing Agent
FOR INFANTS AND PRE-SCHOOL CHILDREN ONLY
DPT POLIO ADSORBED 5 ml
CONNAUGHT
Td POLIO ADSORBED (FOR ADULT USE)
5 x 0.5 ml Ampoules
Tetanus and Diphtheria Toxoids and Poliomyelitis Vaccine Adsorbed (For Adult Use)
Active Immunizing Agent
Td POLIO ADSORBED (FOR ADULT USE) 5 ml
CONNAUGHT
T POLIO ADSORBED
5 x 0.5 ml Ampoules
Tetanus Toxoid and Poliomyelitis Vaccine Adsorbed
Active Immunizing Agent
Dose: 0.5 ml INTRAMUSCULARLY
T POLIO ADSORBED 5 ml
CONNAUGHT

Adsorbed vaccines have been shown to produce an improved serological response compared with the non-adsorbed products.

The use of adsorbed vaccines introduces two important changes in product usage:

- reduced dosage — 0.5 ml
- intramuscular injection

These vaccines will replace the current non-adsorbed (fluid) preparations and are available from your usual source of supply.



CONNAUGHT

CONNAUGHT LABORATORIES LIMITED
1755 Steeles Avenue West
Willowdale, Ontario, Canada M2R 3T4

For additional product information please contact
Medical Department (416) 667-2622, (416) 667-2738
Customer Service (416) 667-2779

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CCPP

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Major new drugs don't just appear. It requires a substantial research commitment to discover, develope and evaluate them. The five leading prescription drugs today did not exist ten years ago. Ten years from now, many leading drugs will be replaced by newer, more effective medicines. Major advances in drug therapy have been a significant factor contributing to the standard of health care in Canada. Drug research means a lot to our continued good health. And that's why Merck Frosst is a leader in Canadian pharmaceutical research.

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